Epidemiology of Cardiovascular Diseases Methodology

hypertension and arteriosclerosis

Guest Editors Herbert Pollack M D and Dean E Krueger



EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

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PREFACE

THE *Conference on Methodology in Epidemiological Studies of Cardiovascular Diseases* was devoted to problems of measurement in selected aspects of these studies Held at the Princeton Inn Princeton N J April 24 26 1959 it was co sponsored by the American Heart Association and the National Heart Institute United States Public Health Service

Subjects considered include criteria for the diagnosis and clinical evaluation of arteriosclerotic heart disease and hypertension dietary physical activity and biochemical measurements assessment of cultural societal familial psychological and genetic influences and general problems of design of studies and analysis of data

This is the report on the third conference co sponsored by the two organizations and directed to research on cardiovascular diseases The First National Conference on Cardiovascular Diseases held January 18 20 1950 in Washington was concerned with the entire range of technical knowledge and research community services and facilities professional education and with all cardiovascular diseases[1] The Conference on Epidemiology of Atherosclerosis and *Hypertension at Arden House Harriman N Y* January 29 February 2 1956 reviewed current etiological concepts in those diseases and tools available for studies of population groups to test those concepts and provide new leads for further investigation By 1957 several groups had either begun or were planning long term studies of cardiovascular diseases in population groups (Representatives of these groups met at the Hotel Beaconsfield Brookline Mass June 17 18 1957 at the invitation of the Framingham Heart Disease Epidemiology Study National Heart Institute to exchange information and consider problems of diagnostic criteria and clinical and laboratory procedures)[3]

With this background of interest and experience in epidemiological research in cardiovascular diseases the cosponsoring organizations felt that the time had come to devote specific attention to problems of measurement faced by individual investigations and to the potential value of being able to combine or at least compare results of several investigators using standard measurements The conference worked toward this goal not with the idea of selecting the best method for measuring any factor which might be important in epidemiological studies of cardiovascular diseases but by considering all available methods giving their judgment about minimum base line measurements which should be included in every epidemiological study of cardiovascular diseases and about optimum measurements which should be made in some studies when the circumstances enable use of these more precise methods

Prior to the conference nine working groups met to consider problems in the subject areas noted above and prepared preliminary reports for presentation to the conference Members of the Committee on *Design and Analysis of Studies* participated in meetings of each of the other groups This was a highly productive preconference activity I wish to express my appreciation to each of the 60 people who contributed to the preconference work as members of committees and especially to the chairmen of these groups to Dr Herbert Pollack chairman of the conference and to Mr Dean E Krueger executive secretary All of these as well as other persons who attended the conference are listed following this preface

The report of each of the nine groups which met prior to the conference was presented and discussed at length in

general e ion Each group augmented by other conference participants who were particularly interested in the subject area al o met eparately to con ider the preliminary report and the di cus ion in general session Revi ed reports were presented at the clo ing general es ion

This publication al o reflects work by committee chairmen and in some in tances committee members after the conference a well as the continuing attention of the editors and technical a i tance from the Heart Informa tion Center National Heart In titute Mr Mary Howes National Heart In titute provided ecretarial ervice prior to and during the conference and typed the manu cript of this report

JOHN W FERREE MD * A ociate Medical Director American Heart Association

REFERENCES

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3 D be T R (Ed) R p f th C f re Lo g d l C d w I S d H t B 6 11 B w kl M (J 1 18) 1 15 (d pl d)

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CHAIRMAN'S ADDRESS

Herbert Pollack, M.D., F.A.P.H.A.

I WANT to welcome you to this Conference on Methodology in Epidemiological Studies of Cardiovascular Disease. One might ask, How did this conference get started and who sparked it into being? The point of origin would appear to be a letter from Dr. A. C. Corcoran to Dr. James Watt written by Dr. Corcoran shortly after returning from a visit to the School of Public Health at the University of Michigan in July, 1958. Dr. Corcoran wrote that while there he had discussed the urgent need for standardization of procedures in cardiovascular surveys. ... This letter set in motion the machinery which resulted in this meeting.

Although the purposes of this conference have been explained to you, I should like to restate them briefly.

One: to set up minimum acceptable base line measures in specific areas, thus providing comparability in epidemiological surveys. Two: to suggest optimum procedures. Three: to define gaps in methodology and to suggest studies to fill these gaps. During the deliberations of this conference we should continuously bear in mind these major objectives which will govern the final report.

The chairman wishes to express at this point his deep appreciation for the hard work of the many persons responsible for the administrative and operational chores involved in a meeting of this type. This conference is sponsored by the American Heart Association and the National Institutes of Health through the National Heart Institute. Mr. Dean Krueger, executive secretary, is really responsible for most of what has taken place. Dr. William Zukel, Dr. John Ferree, and many others have devoted a tremendous amount of time to the organization of this meeting—the happy culmination of which we see here.

In Biblical times the concept of the relationship of the environment to the individual and the individual to the environment was stated somewhat differently than it is today. Formerly the phrase "The world, the flesh, and the devil" was used. Today we discuss the environment, the host, and the cause of the diseases. The health of the community as well as the diseases of the community are expressions of the relationship between the three factors enumerated. Even in Biblical times there was a concept of the epidemiological or the ecological approach to disease.

To fully understand the variations of the incidence of mass disease one must draw upon world experience rather than the small segment represented by a given community. Diseases and disease states show many variations depending on environmental conditions under which they are observed. The epidemiological approach—based upon the ecology of the individual—makes use of these types of data. It uses the methods of all the scientific disciplines represented here today: clinical medicine, statistics, social science, pathology, biochemistry, experimental physiology, *and many others.*

Those attending this conference recognize that in the history of medicine no disease has ever been conquered by an attempt to treat every affected individual. It is only by studying the etiology through the epidemiological approach that man has been able to stamp

out many diseases. It is hoped that this approach can be applied to the problem of cardiovascular disease.

One purpose of this conference is to point out to those interested in this area of *investigation the questions that* remain to be answered. Certain criteria will be set up which can be made applicable to large areas as standard for the collection of data. If we are to compare data from one area of the country with that from another or data from one part of the world with that from another, obviously the e must be collected with such comparisons in mind. Standard used in all studies when reporting deviations from the normal should be mutually acceptable and understandable so that end results can be meaningful in all countries. To use different standards in various parts of the world is like conversing in different languages without a translator.

As chairman I am enthusiastic at the opportunity of working side by side with specialists from the many disciplines represented here. It is a challenge—and also a real problem in coordination. But then the essence of good epidemiological research is the coordination of many specialists toward a common goal. One must not minimize the value of personal views, the concept that permits any person to report, but only certain ones to advise, is unacceptable for this meeting. If it were acceptable it would result in too great a reliance on so called study groups of all types.

While this is a new panel it can also be viewed as a historical extension of *the Brookline Conference. Let us not* therefore fall into the error of many new panels that act as if nothing had ever been done before—perhaps because the continued existence of the problem before the panel is taken by some as an indication of the inadequacy of previous conferences.

The effective results of a conference of this type depend not only on the contributions of each participant but on something even more important, namely the working relationship of each individual to his fellow members and to the group. The value of the final report *could be negated if the individual prob*lems of specialists became isolated from the group and each problem were disposed of in its own way—by experts to be sure—but by experts who only intereste in the special difficulties involved in their own particular area.

Conferences of this type can be extraordinarily useful: not only can they provide us with fresh points of view but they can also provide us with an excellent way of locating talent that would otherwise be unavailable. The number of outstanding individuals with experience in any one field is limited. As a result the same group is called upon time and time again to review these and related tasks. The type of panel present today is somewhat different from the usual one. Usually in panel deliberations the question stands or falls on the skill with which it is presented. Hence there is a premium for quickness of comprehension by the successful committeeman. Here we hope that the more important quality of *reflectiveness* rather than fluency in speaking will predominate.

There will be a further difference from previous panels. Usually panels are expected to adjust differences that exist between participants; therefore it is not surprising to find them ending up with a resolution which is a common denominator rather than a well rounded *creative point of view. I hope we will* not return to the common denominator type of resolution. If we do not, this conference will contribute an important concept to the technic of solving problems.

The development of short term expedients is not the purpose of this conference, nor are we attempting to find Utopia where all questions will be

answered and all problem olved We are not looking for the registration of di enting points of view We do seek from you a significant contribution to the field which will give a sense of direction to the development of epi demiological method for study of the cardiovascular di ea es

In bringing together the variou dis ciplines for this conference we hope that each of you will have the opportunity to pre ent your mo t important con iderations and to under tand the point of view of other di iplines It will be necessary to place a premium on those phases of other di ciplines which can not be most ea ily duplicated by your own Personally I would recommend that you listen particularly to phases of ancillary di ciplines which are unrelated to your own—these are the ones that require integration into your own field of expertnes The peculation which we eek can exi t only when the facts are not known with the development of these fact the area of peculation are graduall narrowed and then di appear

FRAME OF REFERENCE OF CONFERENCE COMMITTEE REPORTS

THE committees took advantage of reports on prior conferences on cardiovascular disease research in the United States cited in the Preface as well as those by Expert Committees of the World Health Organization to which some of the committee reports refer The scientific knowledge of members of the committees however provide the major basis for this report

The committee reports reflect the information most acceptable to participants in the conference and in general their consensus regarding the adequacy and limitations of presently available methods and their ideas about research needed to improve or develop new methods

Credit and responsibility for the content of these committee reports rests primarily with the chairmen and secondarily with committee member and other participants in the conference

A special note is in order about the report of the Committee on Cultural Societal Familial Psychological and Genetic Influences on Cardiovascular Diseases Diverse scientific disciplines —in many instances represented by one person—were included in this group The report is presented as the chairman s interpretation of information provided by members of his committee coupled with his own broad knowledge of the subject It did not seem feasible in the limited time available to attempt to arrive at a synthesis of ideas on methodology in an area of study in which there are so many unknowns

COMMITTEE ON DESIGN AND ANALYSIS OF STUDIES

Felix E. Moore, F.A.P.H.A., Chairman

It is clear that the problem of design and analysis in epidemiological studies of long-term disease is so varied and complex that nothing short of a lengthy treatise could provide adequate coverage. Such a treatise has not yet been written, and its formulation is clearly outside the capabilities of an ad hoc committee meeting for a limited period. The committee has concerned itself, therefore, with a small number of rather general problems which appear to be recurring ones in this type of investigation. These are dealt with under two main headings: I. General Problems of Definition and Design, and II. Measurement Problems. The committee has also considered it necessary to confine its attention to those studies which are based on the clinical or pathological examination of individuals, thus omitting from consideration the types of studies based primarily on information secured by lay interviewers from household informants (morbidity surveys) and the types of studies based primarily on information from death certificates (mortality studies).

I. General Problems of Definition and Design

A. Some General Characteristics of Epidemiological Studies

Many types of studies which have contributed to advances in our knowledge of cardiovascular diseases have been termed "epidemiological."[1] There appear to be common elements of design which characterize these studies and common problems in the interpretation of results which differentiate them from other approaches to the study of disease. The committee believes that it will be more profitable to outline these common elements and problems than to attempt to formulate a narrow definition.

Epidemiological studies have been referred to variously as descriptive studies, population surveys, studies of association rather than causation, and have been contrasted with clinical or laboratory studies or controlled experiments. Each of these terms has connotations which undoubtedly will vary from one investigator to another. By way of clarification of the concept the committee suggests that the following elements are characteristic of epidemiological studies:

1. In an epidemiological study the subjects studied *include not only persons known to have the disease under consideration but also persons who are free (or apparently free)* of the disease as well.* This makes possible the search for factors which differentiate the two groups or, alternatively, the search for factors differentiating the subgroup among those free of disease who subsequently develop recognizable disease from the subgroup of those who do not. A frequent implication of the term

* In order to free the text of this report from the recurring circumlocution "apparently free of disease," the terms "free of disease" or "not diseased" will be used as labels for those persons in whom signs of cardiovascular disease (arteriosclerotic or hypertensive, as appropriate) cannot be observed by standard clinical or laboratory methods of assessment. It is recognized that this begs an important question which is discussed in Section IIA of this report.

clinical study is that it is concerned only with the group which seeks medical attention for disease, yet in many clinical studies a disease group is compared with a control group. The difference, if any, lies in the method by which the study groups are selected and the breadth of generalization which that selection permits. Since epidemiological studies frequently require exhaustive clinical method of evaluation. (See sections IA2 and IID for further elaboration of this point.)

2. The ideal epidemiological study would be based on probability samples from a very large population in order to permit generalization from the study group to the larger population with specifiable limits of precision. It is rare, however, that the ideal approach is possible; the circumstances under which epidemiological studies can be conducted often do not permit the drawing of random samples from the very large population to which it would be desirable to generalize. It is important to recognize, therefore, that generalizability is a relative matter; rarely in *practice* will *generalizations* apply to broader populations without some restrictions. Knowledge of the parent population and the way in which the sample subjects were drawn are essential in evaluating limitations on generalizability in any epidemiological study. This information should be provided in the published report of studies. The extent to which generalizability is required is dependent on the state of knowledge at the time; at an early stage of knowledge a small study on a limited population may provide clues which can be explored in samples from broader population to permit extension of the generalization.

3. The first aim of epidemiological study is to identify characteristics of individuals and of their environment (broadly defined environment includes all agents impinging on the individual) which are associated with the existence or occurrence of disease. These associations can be tested for statistical significance by standard techniques, and it is now generally understood that the acceptance of the finding of significant association does not imply the establishment of a cause and effect relationship. Nevertheless, the search for associations is a search for factors which may be etiologic in the disease, the degree of confidence in which the associations are held, taking into account information from other sources such as hypotheses about mechanisms involved, should point the way toward conclusive studies of etiology.

4. In studies of human populations it is rarely appropriate to study a single factor; usually multiple factors and associations are studied. A number of probable factors in the etiology of cardiovascular diseases have been identified in previous studies. In the search for new factors, those already implicated should, wherever possible, be observed and taken into account in the analysis of the new study. Alternatively, certain variables may be controlled by limiting the study to groups of persons which are relatively homogeneous with respect to these variables, e.g., persons with specific age, sex, race, occupational, or other characteristics.

5. The observational epidemiological study lacks two important elements of the clinical or laboratory experiment. First, no attempt is made to alter the characteristics of the group under study; rather there is dependence on the so-called experiment of opportunity [illegible] which concomitants of variation in the existing environment (external or internal) of the individual are analyzed in the same fashion as the sequelae [illegible] perimentally introduced chang[illegible] controlled laboratory situati[illegible] because no attempt is ma[illegible] specific variables, the [illegible] of randomization of [illegible]

viduals to treatment and control groups is missing from this type of epidemiological study.* For example, in a study of the association of smoking with risk of coronary artery disease, by analogy with the clinical trial, smokers may be regarded as the treated group and nonsmokers as the control group. Failure to randomize places restrictions on certain statistical generalizations and requires that they be considered as approximations to the experimental situation where true randomization is applied. On the other hand, the attempt to control all relevant factors in the experimental situation may well result in the loss of information on important interrelations because the range of environmental factors is artificially limited. This may constitute a severe limitation to generalization.†

B. The Time Reference of Studies: Retrospective and Prospective

The pathologic changes involved in arteriosclerotic heart disease and hypertension develop over a period of years and appear to be influenced by host or environmental factors which exert their force over much of the lifetime of an individual prior to the time the diseases become clinically recognizable. Data pertaining to a substantial portion of the life span of the individual prior to identification of his disease are much more likely, therefore, to yield information of value than contemporary data alone. It is for this reason that time-span studies, either retrospective or prospective, are often regarded as superior to cross-sectional studies. In fact, each of the three methods has both advantages and disadvantages which must be balanced in the individual instance.

The prospective and retrospective approaches will be considered first, with the discussion of the cross-sectional study reserved for a later section (IC).

In the typical prospective study (which is frequently referred to as a longitudinal study or study of cohorts),‡ a population is selected for study without prior knowledge of the disease status of the individuals making up the population. Each individual is examined at the outset of the study and classified as diseased or free of disease. At the same time, data on other individual characteristics which might possibly be related to risk of disease are secured and recorded. Those free of disease are regarded as the population at risk and are observed over some time period. At the end of the period the population at risk can be classified into two groups: those who have developed manifest disease and those who remain free of disease. It is also possible to classify the population at risk into groupings on other factors (e.g., lipid levels, body fatness, dietary patterns) which characterized each individual at the time of entry into the study. If differences in incidence of disease are found in the various groupings on some classification

* It is recognized that there is an area of experimental epidemiology which has many of the aspects of the clinical trial, including randomization. This special type of study will not be discussed in this report.

† For more extended discussions of the points raised in this section and references to the literature, see references 1 and 2.

‡ There is not full agreement on appropriate terminology for describing various types of studies. In this report, prospective and longitudinal are used synonymously for studies in which groups are followed from the time of definition forward in time. The term "cohorts study" has been proposed to describe the prospective study in which specific individuals are followed, in contrast to an alternative type of longitudinal study in which successive samples of an originally defined group are studied rather than identical individuals. (This latter type of design has been discussed in reference 3 and is not further discussed in this report.) Since the term "cohort" in life table analysis implies a group of persons born in the same year whose subsequent mortality experience is described, the term "cohorts study" would appear to be applicable to the type of longitudinal study where individuals of varying ages at entry to the study are followed in time.

the association suggests the presence of an etiological factor.*

In the typical retrospective study one group of individuals is brought into the study because they have exhibited manifest signs of disease. A second group of individuals are selected for study who are free of disease. Often the latter group are matched with the former with respect to age, sex or other factors. Data are then secured on other individual characteristics of the persons in the two groups in respect to life experience *prior to development of disease* or in the case of those free of disease prior to entry to the study. As in the case of the prospective study the characteristics of the two groups are examined for differences which will suggest etiological factors.†

There are many possible variations within these two types of studies but the important difference between the two is that in the prospective study data on the diseased are recorded before the criterion event (or diagnosis) and in the retrospective study after the criterion event (though with respect to a time period before the event). In practice nearly every prospective study makes use of some retrospective data, e.g., a lifetime history of smoking obtained at entry to the study, but the important difference is that it is secured before the occurence of the criterion event.

The retrospective approach contains certain problems of sampling design which may be very difficult though not necessarily impossible to overcome. At any given point in time it may be extremely difficult to secure a representative coronary population. The survivors who are the only ones available for study may be quite different for example from those who died in their first attack. If usual medical sources are used for the selection of the coronary population some important groups of the population may be omitted. It is also difficult to specify the method of sampling for the selection of the appropriate comparison group.‡

Another problem in the retrospective study is that the occurrence of the criterion event may cause the affected individual (or his physician or a family informant) to revise the information that would have been presented in advance of the criterion event. It is for this reason that the burden of proof lies on the investigator in the retrospective study to demonstrate (perhaps by ancillary studies) that the occurrence of the criterion event does not affect reporting of prior events.

The kind of data available for retrospective studies are frequently not determined by the investigator nor recorded with his purposes in mind nor easily subject to validation procedures as are data recorded in a prospective study. Thus the study dependent on past hospital records may encounter frequent gaps and shifts in recording method.

The prospective study encounters other and different sampling problems. One of the chief of these is the problem of nonresponse either in terms of refusal to participate in the initial examination or refusal to participate in the follow-up examination. The expense of the prospective study almost invariably limits the representativeness of the group which can be studied.

There are certain risks of bias in the prospective study in that the process of observation may itself influence the rate of development of disease in the population. There is also the possibility that early findings in the study will cause biases in subsequent observation.

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* Description of three prospective studies in the cardiovascular field will be found in reference 4.

† See reference 5 for description of a retrospective study of this general type.

‡ For extended discussion of sampling problems see references 6 and

Stuhes de igned to a e these ri ks are needed

The co t of maintaining a prospective study in operation for a period of time long enough to provide u eful data and the problem of maintaining continuity of personnel are undoubtedly evere handicaps to it ucces ful prosecution

Both the pro pective and the retro spective tudy are of crvational tudies and neither can demon trate cau ation in the same en e as an experimental tudy The prospective study i theoretically uperior to the retro pective study in ample de ign and in protection again t the ri k of biase in a po teriori ol ervation and recording of data and for these reasons it has been preferred by tati tician On the other hand killed investigators have developed methods for protecting again t many of the dangers of the retro pective study * If these ri k can be minimized by appropriate afeguard the retro pective study will be attractive because of sizable avings in both the length of time required to produce ig nificant finding and in co t

Pro pective tudie can in ome instance achieve ome of the economy u ually attributed to retro pective studies by delaying proce ing of data until it pertinence has been e tabli hed For example in a prospective tudy of total serum chole terol and coronary heart di ea e era for the entire tudy population could be tored and cholesterol level te ted only for ubject in whom the di ease occurs plu a relatively small ample of the va t majority of ubjects in whom it doe not occur

In balance at an early tage of knowledge the retro pective tudy is a relatively quick and inexpen ive but insecure method for gaining in ight into the etiology of di ea e If the findings of such a tudy are challenged on the ground outlined above the challenge can only be an wered by conducting a pro pective tudy But as in the ca e of the moking and lung cancer controver y it is clear that even the prospective tudy is not immune to challenge when offered as proof for cau al relation

C Cross Sectional Studies

In the cro ectional tudy in contra t to the time pan tudies the analy i is ba ed on compari on of observation on groups of individual at a given point in time It i u eful to con ider two type of cros ectional tudies

In the fir t type a group of person with known di ease are available for tudy and a group of persons free of the disea e are elected for comparison Each individual is thus characterized as to presence or absence of di ea e and in addition by contemporary observations on other factor believed to be relevant to the disea e process The interpretation of the results mu t nece arily be ba ed on the as umption that the differences ob erved between the two groups are similar to tho e which would have been found if it had been pos ible to ob erve the groups before the criterion event

This type of tudy differs from the retro pective tudy previou ly de cribed only in the fact that data are ecured by contemporary ol ervation and not by recall While the cro s ection tudy is thu protected against the possible effects of the criterion event on recall thi protection is ecured at the expense of omitting data on the period prior to the criterion event The cros ectional study i subject to the possi bility of bias if the di ea e group ha because of the occurrence of the di ea e shifted it po ition with respect to pre di ease characteristics hifts in characteri tics may be phy iological equelae of the attack it elf or a result of sub equent treatment Thu certain lipid

* Reference 5 pro ides examples f ev ral methods for te tin alid ty of retro pect ve data

level or blood pressure or weight for example might differ from those which existed before overt disease occurred. The cross-sectional study is subject to the same problem of sampling as the retrospective study in that those in the disease group represent only the survivors of some larger group which had experienced disease. The relatively large group of coronary cases which die suddenly *in the first attack*, for example, are rarely included in hospital series. If it should be shown that the sudden death group differed significantly from other coronary cases, then a study based on survivors only would yield a biased finding. Also, as with the retrospective study, it is difficult to specify what non-coronary group is appropriate for comparison because of uncertainty concerning the original disease-free population from which the coronary group arose.

In a second type of cross-sectional study, groups are characterized as to disease prevalence (or incidence) rates and simultaneously characterized in terms of group averages with respect to other factors, e.g., proportion of caloric intake in the form of fats of various types. If differences in prevalence rates *are found to be associated with group* differences in other factors, it may be inferred that the factors have etiological significance. Groups may be chosen on many different grounds. For example, when it is found that groups selected for study on the basis of age and sex *show different* prevalence rates of disease, the inference is made that these factors are significant in assessing risk of disease. It is clear from this trivial example that analysis at this level will not throw much light on differentials in risk within age-sex groups unless individuals can be further subclassified both with respect to disease status and other characteristics. More frequently this approach is used in comparing disease prevalence in groups differing in occupation or in geographic location (with accompanying racial, cultural, or other differences). It is clearly profitable to seek groups differing widely in disease prevalence and to explore other factors characterizing these groups with the hope that factors which differentiate the group may provide leads for further investigation. Frequently a direct interpretation will be difficult because of the confounding of many factors.*

D. Problems of Sampling: Selection of Comparison Groups

In previous sections a number of problems of sampling have been touched upon. It has been pointed out that no population is general or whole in the sense of not having its own peculiar characteristics reflecting factors which may be of importance to the study of disease, such as its prior mortality experience, ethnic origin, age and sex composition, and a wide variety of environmental circumstances. Thus the most defensible sampling method insures only that the sample statistics will provide estimates of the parameters of the population sampled within specifiable probability limits. It seems probable that studies of cardiovascular disease of the depth required by the present state of knowledge will continue to be limited as to scope in both time and area coverage because of cost and limited availability of trained personnel. Under these circumstances the repetition of studies under comparable conditions with well-designed samples and in different places will provide reinforcement of similar findings even though there may be no statistical method for making a probability statement about the combined results.

In a number of international cross-

*This approach, sometimes termed geographical pathology or human ecology, has been discussed in some detail in a publication which became available subsequent to the conference; see reference 8.

sectional studies now being carried out the groups selected for study have been chosen by a method which has been referred to as "chunk sampling."* The chunk may be a circumscribed occupational group (such as firemen in a given locality) or the residents of a small village. Within the chunk an attempt is made to secure 100 per cent coverage in order to avoid the bias of individual selection. Comparisons are then made between similar groups in different countries in order to draw inferences about possible causal factors when differences in disease prevalence are found. This approach has many advantages and permits the carrying out of studies in areas where more extensive sampling would not be feasible. It must be recognized, however, that there are selective factors in affiliation of individuals with occupational groups and that these may vary from area to area. The utility of the chunk sampling approach will be increased as more comparative information is made available, not only concerning variations between chunks in different countries but also between individual chunks within a country and the remainder of the population of that country. Results from studies of this type must be interpreted in terms of present limitations on knowledge of the representativeness of the groups.

In the discussion of the typical retrospective and cross-sectional studies it was pointed out that there are serious problems of sampling in the selection of the appropriate free-of-disease group for comparison with the disease group. These problems are of sufficient importance to warrant further elaboration here. In the traditional design of the experimental study, patients are assigned to treatment and control groups at random before the experiment, and it is this random assignment which makes presently available statistical theory appropriate for analysis. In the longitudinal study the "treatments" are not assigned at random since other individual nonrandom elements come into play in the placement of individuals into "treatment" groups on a factor such as, for example, body fatness. However, in the longitudinal study the population out of which the disease group originated is specified at the onset of the study and can be classified on a single characteristic such as degree of body fatness, from the beginning of the observation. Under these circumstances it is appropriate to test the association between body fatness and risk of disease by testing whether the new cases of disease are distributed among the various body fatness groupings in a manner compatible with the assumption that there is only random variation from a uniform average risk in all groups—which supports the decision of no association. Alternatively, if the distribution of new cases among the various body groupings is such that it would have been very unlikely to occur if there were only random variation from a uniform average risk, then the decision of "significant association" is supported. (It has already been remarked that association does not necessarily support the inference of causal connection.)

In the type of study where a comparison group of free-of-disease persons are selected for contrast with the disease group, there is neither the element of randomization in assignment of "treatment" found in the ideal experiment, nor is there the certain knowledge that the persons free of disease at conclusion of follow-up are the remainder of the original population from which the new disease cases came—the situation which makes permissible the type of statistical test described above in the typical longitudinal study.

There are, in fact, no logically de-

* For a discussion of this approach and general problems in surveys, see reference 9.

fensible rules which can be specified for the selection of a comparison group in the type of retrospective or cross-sectional study where independent selection of diseased and free-of-disease groups is necessary. What can be specified is that the two groups should be as much alike as possible with respect to factors which are known in advance to differentiate the two groups.* The difficulty is to insure that the selection process does not permit the introduction of other factors which would differentiate the two groups and yet be unrelated to the disease process itself. Thus when studies of this type are undertaken a large part of the protection against misleading interpretations must rest on that part of the skill of the experienced investigator—medical or statistical—which is art rather than science.

E The Problem of Nonresponse

General population studies in which clinical methods have been used for diagnosis of disease have rarely secured participation in American populations from more than three fourths of the designated sample. Presently available technic including use of mobile examining units conveniently located apparently are not adequate to raise the response rate above this level.† Incomplete response introduces the strong possibility of bias in result but the nature of this bias has not been adequately studied because suitable means for doing so have not been found. There is urgent need for further methodological study in this area. It is also important that data on response rate be published in detail with the report of each study.

The completeness of examinations in terms of procedures to which the subject is asked to submit and the time required to carry them out appears to discourage participation. The desirability of completeness of information must therefore be balanced in any study against the desirability of a high rate of response.

In longitudinal studies where the major comparisons are among groups of persons who actually participate initial nonresponse is less serious than in cross-sectional studies provided that virtually complete follow-up of the initially respondent group can be secured. A high drop-out rate subsequent to initial response could however be related to health status and thus introduce serious bias. Fortunately it has been demonstrated in several longitudinal studies that while it was impossible to secure complete response from the original sample it has been much less difficult to secure reexamination on the original respondent.

Four types of information are useful in evaluating the effect of nonresponse in both longitudinal and cross-sectional studies:

1 Information about the individual health status as reported by him in home interview by a lay interviewer—obtained prior to the invitation to participate in medical examination procedure.

2 Mortality data and data from hospitals and physicians on nonparticipants for comparison with similar data for participants.

3 Within the participating group an analysis of health status among respondents classified according to the amount and type of effort required to secure participation.

4 Special sample studies of nonrespondents possibly using some minimal clinical observation in the home.

II Measurement Problems

A *Definition of the Disease Being Studied*

Our concept of disease changes when methods available for diagnosing

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* Some methods for statistical handling of data where matched controls are used in studies of this type are described in reference 10.

† Preliminary report from the National Health Survey have indicated that it may be possible to secure higher response rates in [illegible]. Continued methodological investigation is being undertaken.

disease change. The decision to make an epidemiological study ordinarily implies that there are available sufficiently precise methods of diagnosis to permit the identification of cases of the disease under study. In this respect the study of hypertensive and atherosclerotic cardiovascular disease is beset with serious problems for lack of objective criteria for identification. The evaluation of blood pressure level is difficult enough. But even granting a reliable pressure evaluation, there appears to be little unanimity as to the other measurable characteristics which should be assessed in order to classify a person into the groupings "hypertensive disease" or "not hypertensive disease." Similarly, with respect to coronary artery disease, while the evaluation of the frank coronary attack can undoubtedly be made with relative precision, there appears to be no adequate method for estimating the extent of advancement of the underlying atherosclerotic process. In longitudinal studies as well as in clinical experience, a significant proportion of subjects found to experience frank coronary events have been classified as apparently free of disease at examination not long before the event. Cross-sectional studies miss such cases entirely.

The existence of this problem has led to what might be called the "Substitution Game," in which blood pressure level is substituted for hypertensive disease or serum cholesterol level for coronary artery disease. It would appear that these substitutes can at best be only crude indexes of the diseases which it is desired to study and their uncritical use may obscure important relationships.*

It seems clear that better methods of diagnosis adaptable to the needs of large-scale studies need to be developed. In any event, the methods employed in current studies should be explicitly described and knowledge of their limitation should be taken into account in interpreting results.

B. Validity of Measurements

A measurement procedure is valid if it measures what it purports to measure; a procedure is reliable if it gives the same results when used repeatedly in the same situation (i.e., when it is reproducible). A measurement procedure may be valid even though its reliability is low; a highly reliable (or reproducible) procedure may be of low validity.

The validity of a measurement, whether of the existence of disease or of some characteristic of an individual (physiological, biochemical, environmental, and so forth), is relative. Validity is often judged qualitatively but should be quantified whenever possible. For example, a given ponderal index based on some ratio between weight and height may be considered a good index of fatness but can be checked against the more nearly exact measure of underwater weighing. Two-stage sampling is useful in checking the validity of a convenient, relatively inexact test applied to an entire study group by subsequently applying a finer but less convenient measure to a subsample.

C. Reliability (Reproducibility) of Measurements

There are two factors which affect reproducibility of biological measurements—variability in the measurement process itself and individual biological variability. The former can often be controlled to some extent provided that the investigator is forewarned of its existence by routine reproducibility studies. An investigator can rarely control individual biological variability.

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* It is not intended to imply that the descriptive epidemiology of blood pressure or cholesterol level will be unprofitable. At the present stage of knowledge such studies may make valuable contributions to the understanding of disease.

he can only reckon with it in his analysis but again only if he has adequately evaluated it

Every study should make some provision for tests of reproducibility of at least selected types of measurements on samples of subject throughout the course of the study The essential factor in such test is the independent application by two or more person of the same procedure to the same object of study whether the object of study be a specimen of serum an x ray film or a subject s description of his symptoms With advance planning incorporation of such tests is feasible though it is recognized that tests of particular kinds of measurements are time consuming costly and not without technical problems in execution An attitude of unquestioning confidence in procedures customarily used may be a major obstacle It would be desirable to establish agreed upon tolerance levels of measurement error for those measures common to epidemiological studies in the cardiovascular field

Individual biological variability is much more difficult to evaluate than simple laboratory reproducibility yet it may be much more important in intraindividual comparisons in longitudinal studies There is need for more complete documentation of individual variability for many widely used measures and in some instances this will require the setting up of special studies The committee notes that other committees of the conference have considered this problem in their report

D *Minimum Base Line Measures and Standard Methods of Presentation*

The committee believes that the epidemiological study of cardiovascular disease will be more productive if steps are taken to secure a greater degree of comparability between the studies which are being carried out by investigators in different population groups One requirement for comparability is agreement among investigators to include in each study a specified minimum set of measurements to be carried out under standard specifications A second requirement is that published reports of studies present these minimum data in some standard format (Alternatively it could be agreed that standard tabular material be deposited with the American Documentation Institute with the deposit noted in the published report) The committee believes that the progress made by the other committees of the conference toward agreement on standard patterns in several areas of investigation is evidence that these aims are achievable and that they can be achieved without putting any undue burden on the individual study or restricting the freedom of the individual investigator The committee recommends that the sponsoring organizations consider setting up a continuing group to make recommendations in these areas and to subject these recommendations to periodic review and revision as required by changing development in the field

REFERENCES

COMMITTEE ON CRITERIA FOR DIAGNOSIS OF DISEASE AND CLINICAL EVALUATION

Joseph T. Doyle, M.D., Chairman

SUBCOMMITTEES ON CLINICAL EVALUATION, BLOOD PRESSURE MEASUREMENT, AND ECG INTERPRETATION

THIS report summarizes the deliberations of three subcommittees which considered the definition and the clinical evaluation of ischemic heart disease and of hypertensive disease, the use of electrocardiography in epidemiologic studies, and the measurement of arterial blood pressure. An attempt is made to offer realistic recommendations concerning diagnostic methods. The numerous lacunae in our knowledge of degenerative heart disease are urgent indications for further research. The committee feels that epidemiologic surveys offer an unusually good opportunity for research in many levels and strongly recommend that such opportunities be exploited.

Epidemiologic studies are concerned with the incidence and prevalence of diseases in population groups rather than in individuals. The occurrence of disease is then correlated with other characteristics of the population. What is needed is a reliable index of disease which will identify the same proportion of cases of disease in various populations rather than a method of locating every single case of disease. An objective method such as electrocardiography which is relatively free from falsifying factors can give a better index of disease rates than the subjective manifestations of the anginal syndrome which may identify larger numbers of cases but are affected by individual differences unrelated to the disease being studied.

Ischemic Heart Disease

Definition—Consistent with the recommendation of the World Health Organization Study Group on Atherosclerosis and Ischemic Heart Disease, the term ischemic heart disease will be used. The definition is as follows:

> Ischemic heart disease is defined as the cardiac disability, acute and chronic, arising from reduction or arrest of blood supply to the myocardium in association with disease processes in the coronary arterial system. The two main pathological processes involved are (a) atherosclerosis of and (b) thrombosis in these vessels. The same processes may be responsible for atherosclerotic and ischemic cerebral and peripheral vascular disease.[2]

The classification recommended by the WHO Expert Committee on Cardiovascular Diseases and Hypertension is endorsed with a number of modifications which are contained in the following extract. The principal manifestations and clinical syndromes of ischemic heart disease are as follows:

I. Myocardial Infarction

(a) Definite Myocardial Infarction—A disease due to obstruction of the coronary circulation and causing necrosis of a macroscopic circumscribed area of myocardium. Such an area will, if death does not ensue, undergo fibrosis. The well known signs and symptoms of acute myocardial infarction will rarely be encountered in field studies. The diagnosis of previous acute myocardial

infarction is ba ed on these two features

(i) Hi tory—A lear history gi en by the patient of the sudden le s often of the g adual onset of severe chest pain or discom fort usually at rest and located a in anginal syndrome (2a below) frequently associated with va omotor collapse and often requiring prolonged bedrest If the pat ent was hos pitalized the information obta ed f om hos pital records should be separately entered so a not to bias comparisons with result f om a eas where such informati n cannot be obta ned

(i) Electrocard ogram — Serial electro-cardiograms taken during the acute phase of myocardial infarction are usually conclu e eviden e of the lesion The electrocardiogram often reveals stigmata stron ly su estive of or diagnostic of old myoca dial infarction An example of some tentat e criteria for the recogn tion of old myocard al infarction is iven in Appendix A Techni al a pe ts of electrocard o raphy are di cu ed in a sub sequent sect on of this report

(b) Possible Myocardial Infarction —The history is not as clear cut as in definite myocardial infarction but in cludes pain or discomfort similar in *location but more inten e and/or of* longer duration than in anginal syn drome (see 2 below) The electrocardio gram i not normal but is not typical of definite myocardial infarction

2 Anginal Syndrome—It has been argued against the use of this syndrome that it is entirely subjective and de pends on the ob erved and the ob erver It is felt however that the manner in *which the patient describes anginal pain* is o characteristic that it cannot be con sidered only subjective and warrants the diagnosis of anginal syndrome as a ubcla ification of ischemic heart di ea e Due care must be taken to recognize the exclusion categories (see 2c below)

(a) Definite Anginal Syndrome—A discomfort or pain occurring across *both sides of the anterior chest wall or* located centrally in the ternal region brought on by effort e g exercise emo-tion exposure to cold and wind It may radiate to the left arm or both arms the shoulders the neck or jaw It is pontaneously described as press ing tight heavy constricting or crushing or as numbing or burning It is usually relieved within a few minutes after cessation of effort or of taking sublingual nitroglycerine Cases of angina at rest will rarely be encountered in field studies

(b) Possible Anginal Syndrome—

(i) Di comfort or pain as in d finite anginal syndrome but be inn ng in any of the site of radiat on mentioned.

(ii) Discomfort or pain as in definite anginal syndrome but commencing in the left or right anterior chest or in th epi gastrium

(iii) Discomfort or pain as in definite anginal syndrome whi h may sub ide d pite continued effort

(c) Exclu ion Categories—

(i) Discomfort or pain as described above occurring aft r es ation of effort as con trasted with discomfo t occurrin during effort e g in anxiety states

(ii) Discomfort or pain a described above o curring only n elation to meals and posture e g hiatus hernia

(iii) Di comfort o p n s describ d abo e but related only to pecial mo ements and positions of the bo ly e g arthritis fibrosit s

(iv) Stabbing or lancinating p n n the region of the left fre st e g in anxiety tates

( ) Localized or general ch t nd/or arm di omfort or pa n d e to thoracic outlet or hype abduct on syndrome

3 Sudden Death—At the present *time there is insufficient quantitative* evidence to ju tify the use of udden death as an index of the frequency of i chemic heart di ea e Except for pecial tudies this term hould be used in the en e of instantaneous death Sudden death hould become a u eful index if quantitative e timates can be obtained in un elected populations of the relative numbers of deaths due to *i chemic heart di ease and to other* vascular cata trophes This problem i con idered in detail in the Report of the Subcommittee on Morphology

1 Congestive Heart Failure—A complex syndrome manifested by dyspnea, diminished exercise tolerance, pulmonary congestion, water and salt retention, hypervolemia, venous hypertension, splanchnic congestion and peripheral dependent edema. In the absence of other etiologic factors it is often assumed that congestive heart failure is due to diffuse myocardial damage caused by coronary artery occlusion. This assumption is unfounded. Chronic heart failure cannot, therefore, be considered *a reliable index of ischemic* heart disease.

The following comments were made by the committee on diagnostic methods:

1 *History—In the absence of any* other information it must be assumed that a history of *anginal* syndrome or past myocardial infarction can be reliably obtained only by a physician. There is no information concerning the reproducibility or the reliability of such histories taken by physicians of varying levels of training and experience. It must also be conceded that the accuracy of a history of ischemic heart disease obtained by a specially trained lay interviewer has never been evaluated. This possibility deserves intensive investigation for use in epidemiological studies. There is sufficient experience with self-administered questionnaire to condemn their use in field studies.[3]

2 Physical Examination—There are no readily *discernible abnormalities* characteristic of ischemic heart disease. *It is, however, possible to detect evidence* of atherosclerotic obliteration of *other vascular territories, such as in* the brain, retinal vessels, and the lower extremities. This information may be epidemiologically just as important as evidence of ischemic heart disease.

3 Electrocardiogram—It is a truism that the electrocardiogram does not identify atherosclerosis but only its myocardial ischemic complication. A majority of individuals with the anginal syndrome exhibit normal resting electrocardiograms.[4] An unknown number of individuals recover from acute myocardial infarction with no residual electrocardiographic abnormalities or with intraventricular conduction defects not usually ascribed to myocardial infarction.[5]

There is increasing indication that an abnormal electrocardiographic response to stress is valuable evidence of ischemic heart disease. *If* time and budget permit and if adequate medical *supervision is available, it is suggested* that an electrocardiographic stress test *be incorporated in some epidemiological* studies. It must be recognized that such *test carry a small but definite risk.* The diagnostic criteria of an abnormal electrocardiographic response to exercise proposed by Robb and Mattingly are *endorsed.*[6]

Hypertensive Disease

The following appears to be a satisfactory definition of the hypertensive process:

> The term hypertensive disease is synonymous with essential hypertension and should properly be restricted to designate the as yet unidentified physiological disturbance (or disturbances) characteristic of this disease and which leads ultimately to elevation of diastolic and systolic blood pressures, anatomical changes in the *vascular tree and functional* impairment of the involved tissue. Hypertension is the earliest clinically recognizable disturbance and results *from constriction of* the peripheral arterioles, thus constriction *leading to an increase in the total effective* peripheral resistance and hence to elevation *of diastolic and systolic blood pressures.* Hypertensive disease is considered to be a clinical entity on which an unknown pressor mechanism initiates arteriolar vasoconstriction, elevated blood pressure and vascular sequelae. Hypertension as such like arteriolar changes is conceived to be a sequela appearing during the progressive development of the disease.[7]

Blood Pressure Criteria—It is advocated that cumulative frequency distributions and curves be used to report the

level of arterial blood pressure found in any defined population these provide the best way of comparing populations It is recognized that clinical usage demand arbitrary criteria of normal and of abnormal arterial blood pressure The following criteria are therefore suggested as a supplement to but not a a substitute for cumulative frequency curves The proposed numerical values can obviously be adjusted to suit the needs of any particular investigator

(a) Normotension—Systolic blood pressure below 110 mm Hg *and* diastolic blood pressure below 90 mm Hg i e *both below*

(b) Hypertension—Systolic blood pressure 160 mm Hg or over or diastolic blood pressure 95 mm Hg or over i e either one or both at or above the specified level

(i) Systolic Hypertension—Systolic blood pressure 160 mm Hg or over *and* diastolic blood pressure *under* 90 mm Hg

(ii) Diastolic Hypertension—Systolic blood pressure *under* 140 mm Hg and diastolic blood pressure 95 mm Hg or more

(c) Borderline Hypertension—This is *the residual category i e the systolic* blood pressure is below 160 mm Hg *and* the diastolic blood pressure is below 95 mm Hg but they are not simultaneously below both 110 mm Hg systolic and 90 mm Hg diastolic Note that the diagnosis of hypertension is based on either or criteria while normotension requires that both the systolic and the diastolic reading be below the cutting points

When multiple determinations are made the assignment should be based on the first determination or on the mean[8]

The following general statements can be made concerning *clinical evaluation* of participants in epidemiological studies

1 Hypertensive Disease Uncomplicated—A the term implies consistently elevated arterial blood pressure is the only deviation from normal No symptoms characterize this phase Complete clinical evaluation requires the exclusion of *visceral involvement and of* causes of secondary hypertension Since secondary hypertension is rare it would seem unnecessary in epidemiological studies to make special efforts to identify such cases

2 Hypertensive Disease Complicated—This term implies visceral involvement which depending on the degree of organ compensation may or may not be characterized by symptoms The vascular territories most commonly affected by the hypertensive process are in the heart the brain and the kidneys Marked elevations of the diastolic blood pressure accelerate and aggravate atherosclerosis[9] The definition of hypertensive heart disease is inevitably circular since it is dependent on the demonstration of what is considered to be an abnormally elevated blood pressure associated with signs and ultimately symptoms of an increased left ventricular work load In many instances the visceral complications of *hypertensive disease may be due to* ischemia consequent to atherosclerotic thrombotic vascular occlusion The following clinical and laboratory procedures are suggested for field use

(a) Heart—History and physical signs of (paroxysmal) left ventricular failure Radiologic evidence of early left ventricular enlargement is notoriously unreliable Electrocardiographic evidence of early left ventricular enlargement is likewise unreliable Large QRS voltages in youth and early adult life cannot be accepted as testimony of left ventricular enlargement. There is poor correlation between th x ray a d *the electrocardiogram in* early left ventricular enlargement

(b) Brain—History of or neurologic residua of a previous cerebrovascular accident. History of hypertensive encephalopathy Retinopathy fundoscopy is extremely fe bl in the field and should at least distinguish normal o mildly abnormal eyes and fr m grossly abnormal employing the Keith Wagener classification[10] U d r som cir u

stances it may be possible to take fundal photographs as an objective record.

(c) Kidney.—There are no satisfactory field methods for estimating renal function. If orthostatic proteinuria be excluded, proteinuria is reliable evidence of renal functional impairment. Microscopic examination of the centrifuged urinary sediment is desirable. Cylindruria may be taken as evidence of renal tubular damage. Pyuria in the male is prima facie evidence of genitourinary infection.

3. The Prehypertensive State.—The existence of this phase is theoretical. There is no evidence that labile arterial blood pressure necessarily presages later hypertensive disease.[11] Tests for vascular hyperreactivity such as the cold pressor test are of no particular diagnostic value and are of unknown prognostic significance due to lack of prolonged follow-up data.[1]

Notes on Technical Methods

1. Measurement of the Arterial Blood Pressure

Instrumentation.—The "Recommendations for Human Blood Pressure Determination by Sphygmomanometer" sponsored by the American Heart Association are strongly endorsed[13] with the exceptions noted below.

It is felt that the following items merit emphasis. It is recommended that a cuff 12-14 cm in width be used; the cuff should be so designed that closure and inflation will exert uniform tension over the whole width of the cuff. Where large numbers of measurements are to be made in a short time consideration should be given to the use of a pressure reservoir to inflate the cuff. The mercury manometer is the standard of calibration. The zero should be clearly visible; the upper end of the glass tube should be freely vented. Aneroid manometers are acceptable if checked frequently (every few days) against a mercury column. The tendency of observers to round off manometric reading is recognized. It is suggested nonetheless that the observer read the scale to the nearest even number. Objective automatic methods of measuring and recording the arterial blood pressure should be well within current technical capability and are highly desirable to avoid the problem of observer bias. Despite the official recommendation that the arterial diastolic pressure be taken as the point of disappearance of the Korotkow sound, there is substantial evidence that the point at which the Korotkow sound becomes muffled may correspond more accurately with the true diastolic pressure.[14-16] It is therefore recommended that both points be routinely recorded. For the present, the point of disappearance of Korotkow sounds should be used as the diastolic pressure for statistical purposes.

The Observer.—It is self-evident that if the auscultatory method of sphygmomanometry be used the observer must have adequate hearing. It is suggested that in epidemiological studies the observer should present a normal complete audiogram as a preliminary qualification. An acoustically acceptable stethoscope should be used. It would be highly desirable for the examiners in all population studies to practice together on the same subject until a satisfactory uniformity of blood pressure measurement had been achieved. It would likewise be highly desirable for similar interstudy comparison to be made. To both these ends it is hoped that audiovisual training devices may soon be fabricated. The clinically traditional use of cutoff points to discriminate between normal and abnormal levels of blood pressure inevitably creates observer bias, as evidenced by anomalies in life insurance statistics and the universal tendency of numerical values for the diastolic blood pressure in particular to cluster at certain points.[17] This problem is so acute that serious consideration might

be given to the use of off et manometer cales to give a purious reading later decoded by the statistician Provision should be incorporated in all tudies to code the ob erver o that the source of po ible systematic deviations may be identified Since however the level of the arterial blood pre sure may normally fluctuate widely[18] ince almo t all proposed criteria di tingui h between dia tolic normotension and diastolic hyperten ion on differences of only a few mm Hg ince as previously noted the indirect measurement of dia tolic blood pre ure is uncertain unreliable and subjective and ince there is no predictable as ociation between the level of the arterial blood pressure and the pre ence of vascular damage the abandonment of arbitrary and rigid cutoff points to di criminate between normal and abnormal levels of arterial blood pres ure is advocated It is felt that proper training and sound motivation are more important than the professional background of the individual who measures arterial blood pressure in population surveys

The Observed—It is probable that the casual blood pres ure is most often measured with the ubject in the eated position The arm must be at the ame level as the heart There may be ome advantage to measuring the blood pressure when the ubject is upine since the arm is then at heart level and ortho tatic hypotensive influences often exaggerated by antipre or and other drug are abolished The dia tolic pressure is less affected by changes in posture The systolic pressure may however be considerably affected by change in posture so that five minutes hould elap e before it is mea ured[19] More comparative mea urements of the arterial blood pres ure in the supine itting and even tanding positions are required The minimum clinical data that hould be recorded include the sex age height and weight and pulse rate of the ubject Mo t hypertensives under treatment seem to be ignorant of the exact nature of their medication It seems nonetheless desirable to inquire of all ubjects whether medication is being taken and to record whatever information is elicited The extent to which obe ity of the upper arm may invalidate the indirect measurement of the arterial blood pres ure is not completely known For thi reason it would be worth while when fea ible to make a comparative measurement of blood pre sure in the forearm[, 1] No definitive statement is pos ible on the optimal number of blood pressure mea urements to be taken There is ome evidence that when taken in rapid (30 econd) sequence there is a ucces ive decline of the second and third reading and that the third reading is fairly representative of tho e made sub equently When multiple mea urement of the arterial blood pressure how rea onable con istency the use of average values for stati tical purposes is probably valid

II Electrocardiography

The Electrocardiogram—The electrocardiogram is an objective record of bioelectrical phenomena Strictly peaking anatomic inferences should not be based on this record Practically the diagno tic interpretation hould be made only after collation of all clinical data

The ECG plays a small and uncertain role in epidemiologic tudies of cardiovascular di ease For example in atherosclerosi it will confidently identify only that small per cent of cases of coronary artery athero clero is where frank myocardial infarction has taken place Criteria for identifying normal from abnormal QPS items are reasonably reliable in many in tances with the notable exception of QRS criteria for left ventricular hypertrophy S T and T criteria for normal and abnormal are much less reliably known The

committee is of the opinion that while large ECG surveys may usefully lend themselves to identifying the normal versus abnormal ECG they do not lend themselves reliably to identifying specific disease. Furthermore while criteria for the normal ECG are reasonably reliable in the age range 10-60 years other age groups have not yet been adequately studied in this regard.

Direct writing electrocardiographs are suitable for population survey but should be frequently checked to insure the accuracy of paper speed and of calibration voltage, stylus cleanline, centering and excursion, vacuum tube stability and so forth. Standard electrode jelly or paste should be used as the electrolytic contact agent although plastic electrode jelly is acceptable.

Lead Selection—Informal polls indicate that electrocardiographers consider the 12 lead (three bipolar and three unipolar limb leads and six or seven precordial V leads) electrocardiogram the diagnostic standard. There is, however, no evidence that the 12 lead electrocardiogram is essential to adequate diagnosis. No more information is contained in unipolar than in bipolar limb leads or vice versa. Conventional precordial lead placement is arbitrary and presents no intrinsic merit save that of general usage. Indeed the placement of precordial leads at the three, four and five positions is subject to anatomical variation and particularly to technician error. The potential gain in ease, speed and money commend the study of the value of limited numbers of electrocardiographic leads.[7]

The Electrocardiographer—Conventional training in electrocardiographic interpretation requires an apprenticeship of a year while competence can be maintained only by continuing experience. Relatively little is known on either an individual or a group basis of the accuracy, reproducibility and reliability of electrocardiographic interpretation. If large population studies are to be conducted these questions must be answered. In addition means must be devised to cope with the enormous numbers of electrocardiograms taken in such studies. Unquestionably a competent electrocardiographer could rapidly and accurately sort electrocardiograms into normal, borderline and abnormal groups up to the limit imposed by fatigue. It is felt that intensive investigation should be made of the problem of developing generally acceptable criteria of electrocardiographic interpretation simple enough but yet sufficiently accurate to be used effectively by a physician or by a technician not specially trained in electrocardiography. The use of simplified improved lead systems is particularly germane to the problem. If as seems likely electronic computers come to be used more commonly in biological investigation the development of suitable electrocardiographic diagnostic criteria will be essential to intelligent programming of such instruments. The Laboratory of Physiological Hygiene of the University of Minnesota with these purposes in view has devised a set of criteria for the electrocardiographic diagnosis of myocardial infarction (Appendix A).

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APPENDIX A

Excerpt from
Classification of the Electrocardiogram for Epidemiological Studies

This excerpt is presented as an example of the kind of criteria for old myocardial infarction which can be constructed based on electrocardiographic surveys of large groups of persons. The examples pertain to resting electrocardiograms taken in the supine position on adults under the age of seventy. Further information about the complete classification can be obtained from the author.

A. QRS Criteria Type I (Myocardial Infarction)
(Q must be 1 mm or more to be designated as such.)

1. Q/R ratio of 1/3 or more in any of leads I, II, V_2, V_3, V_4, V_5, V_6, or if the transition zone is to the left of V_5 in lead V.
2. Q wave duration of 0.04 second or longer in any of leads I, II, V, V_2, V_3, V, V_5, V, and if R is plus 3 mm or more in aVL.
3. Q wave duration of 0.05 second or longer in lead III or if R is plus 3 mm or more aVF. (Some Q must be present in aVF.)
4. QS pattern (absent R wave) in any of leads V through V_6 when an R wave is present in the adjacent precordial lead to the right.

B. QRS Criteria Type II
(Q must be 1 mm or more to be designated as such.)

1. Q/R ratio of [illegible] to 1/3 in any of leads I, II, V_2–V_6, or if right ventricular hypertrophy is not present in lead V_1.

Prepared by Henry Blackburn, Ernst Simonson, Ancel Keys, et al., Laboratory of Physiological Hygiene, University of Minnesota. The complete criteria include most electrocardiographic abnormalities of importance for epidemiological studies.

2. Q wave duration of 0.03 to 0.04 second (in any of lead I, II, V_1-V_6 and if R is plus 3 mm or more in aVL).
3. Q wave duration 0.04 to 0.05 second in leads III or aVF. (Some Q must be present in aVF.)
4. Q amplitude of 5 mm or greater in leads III or aVF when an R wave is present.
5. QS pattern in V_1-V_3 in the absence of left bundle branch block and left ventricular hypertrophy.

SUBCOMMITTEE ON MORPHOLOGY

David M. Spain, M.D., Chairman

Introduction

THIS report presents the combined effort of the committee and the conclusions represent complete agreement among the members of the committee. It is particularly worthy of mention that basic agreement was rapidly reached in all major aspects of this report. Comparison with the conclusions reached by the WHO Study Group on Atherosclerosis also reveal major similarities with this committee's conclusion. The recognized difficulty in epidemiologic studies on coronary atherosclerosis in live population groups is the inability to obtain precise measurements of the degree of atherosclerosis that may be present in any of the individuals studied. In autopsy studies this difficulty is to a great extent eliminated but studies on autopsy populations suffer from lack of ability to properly generalize the findings to the population as a whole. Nevertheless it is believed if comparable post mortem methods are used in different areas of the world, a valuable contribution may be made to further the understanding of the pathogenesis of this disease.

Definitions

The definition of the atherosclerotic lesions to be measured was similar to that agreed upon by the WHO Study Group in 1958.* This definition is as follows:

> Atherosclerosis is a variable combination of changes of the intima of arteries consisting of focal accumulations of lipid, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with medial changes.*

The lesions to be considered within this classification may be subdivided or classified in several different ways. The manner of subclassification is less important than the preciseness and clarity of the definitions. Some will classify the various lesions into fatty or lipid streaks, fibrous plaques, atheroma, and complicated lesions. The complications include hemorrhage into the lesion, superimposed thrombi, ulceration and calcification. Others suggest that the lesions be divided into lipid streaks, fibrous plaques, complicated lesions and calcifications; definitions of these classes of lesions are given in Appendix A. Listing of these lesions in the above order does not necessarily imply any exact biological sequential relationship. It is also understood that the term fibrous plaque does not preclude the presence of lipid complexes within its depths. The importance of defining and

* Classification of Atherosclerotic Lesions (Report of a Study Group). WHO Tech. Rep. Ser. No. 143, 1958.

subclassifying these lesions resides in the fact that in any measurement or grading system the lipid streaks should at least be clearly delineated from the others.* In measuring the surface area of involvement in the aorta or coronary artery, 40 per cent involvement with only lipid streaks may have an entirely different significance than a similar degree of surface involvement with any combination of the other classes of lesions.

Vessels to Be Studied

The coronary arteries and aorta should be examined in every instance. *It is not feasible to consecutively study* the cerebral vessels because in this country at least post mortem permission for such examination is often not obtained. There are also greater technical difficulties for making measurements of the degree of atherosclerosis that would interfere with a reasonable ability to compare one study with another. It is not sufficient to either examine the coronary arteries or the aorta alone. The findings of the degree of atherosclerosis in a series of aortas do not necessarily parallel those in the coronary arteries. Sex, race, age and geographic differences also affect comparability of the degree of atherosclerosis in the aorta with the amount of atherosclerosis in the coronary arteries (see Table 1). Therefore, as a minimal objective in order to obtain a more meaningful over-all picture, at least both vessels should be studied. *Where routine* and consecutive brain examination can be made and where sufficient attention can be given to the proper examination and grading of cerebral atherosclerosis, it is of course highly desirable to do so. Any such study on cerebral atherosclerosis, however, must take into account the fact that cerebral ischemia may develop as a result of atherosclerosis in carotid artery branches entirely external to the skull while the intracerebral vessels may show comparatively little change.

The examination of other vessels in a piece-meal fashion, such as mesenteric arteries or renal arteries, would not contribute any significant information to the over-all picture. At present, legal, religious and embalming obstacles preclude the possibility of routine examination on all the major vessels of the body.

Preservation and Records

The conditions under which examination and grading of the vessels are conducted will determine to a great extent the objectivity, accuracy and comparability of the findings. Whether or not the specimens should be examined in a fresh or fixed state will depend upon the particular circumstances under which the study is being conducted. Whichever the method, it should be consistently employed throughout the study because there is evidence to indicate that variations in grading, particularly as regards coronary arterial luminal size, exist between the fixed and unfixed state in the same specimen. Provision should be made for preservation and semipermanent storage of the vessels. *A practical method* utilized by one member of this committee is excellent for this purpose.† Permanent storage of the vessels is not always feasible because of expense, personnel and time-consuming effort involved. In any event the findings should always be reduced

* Strong, J. P., McGill, H. C., Jr., Tejada, C., and Holman, R. L.: The Natural History of Atherosclerosis: Comparison of the Early Aortic Lesions in New Orleans, Guatemala and Costa Rica. Am. J. Path. 34: 731–744 (July-Aug.) 1958.

† Holman, R. L., McGill, H. C., Jr., Strong, J. P., and Geer, J. C.: Techniques for Studying Atherosclerotic Lesions. Lab. Invest. 7: 42–47 (Jan.-Feb.) 1958.

Table 1—Relative Degree of Atherosclerosis in Aorta and Coronary Arteries in Consecutive Autopsies of Sudden Death (M F Cases) from Natural or Accidental Deaths

	Total Cases	A>C	A=C	A<C
Age group 30-50 years				
Females	76 (100 %)	32 (42 %)	28 (37%)	16 (21%)
Males	147 (100%)	11 (%)	49 (34%)	87 (59%)
Age group 51 70 years				
Females	72 (100%)	6 (36 %)	28 (39 %)	18 (25%)
Males	165 (100%)	35 (21%)	61 (37%)	69 (42%)

A>C Aorta has a relatively greater degree of atherosclerosis than coronary arteries
A=C Aorta has an equivalent degree of atherosclerosis to that of coronary arteries
A<C Aorta has a relatively lesser degree of atherosclerosis than the coronary arteries
(Spain D M and Bradess V Unpublished data from Westchester Medical Examiner Coronary Study)

to some form of schematic diagram which can be permanently kept The elaborateness and detail of such a diagram will vary with the needs and design of the particular study (Examples of simple and more detailed diagram are listed in Appendixes B 1 B 2 and C)

Examination of the Vessels

The examination interpretation grading and measurement of the lesions in the vessel should be performed by competent pathologists well versed in the various lesions of atherosclerosis Preferably one examiner should carry out the entire study When this cannot be done a team of examiners should be trained in advance so that their measurements cross check with each other in order for the findings to be reasonably consistent and reproducible

Unbiased grading is difficult in the absence of a coding system Sometimes the situation demands that a specimen be examined immediately at the site of autopsy In such situations it is sometimes impossible to conceal age sex race and so forth But when possible the project should be so designed that the grading and examination can be determined in completely coded material

The method of grading lesions depends to some extent on the technic employed in dissecting the vessel The standard method of examining coronary arteries—cross sectional cuts or longitudinal dissection—are acceptable If the cross sectioning method is used these should be performed at intervals no further than 3 mm apart It is recognized that the WHO report suggests a 5 mm difference as being sufficient but it requires very little extra effort to reduce the interval and in the experience of some an interval as wide as 5 mm can miss a significantly large number of thrombi or occlusive atherosclerotic plaques In the longitudinal method the vessel is opened as far as possible with small coronary dissecting scissors The quantity and quality of the surface area involved is then recorded The three major coronary vessels must be examined

The aorta should be examined by a lengthwise opening and then spread flat The entire aorta should be described but for grading purposes the surface area between the upper margin of the first intercostal artery orifice and the bifurcation into the iliacs should be

considered Some have recommended that the circumference of the aorta hould be measured at various levels This information would not appear to contribute to the olution of any of the desired objectives and would only add unnecessary detail to the examining procedure

Grading

It matters little as to what terminology is used in the grading method provided the terms are clearly defined within an accurate and clear frame of reference If this procedure is followed regardless of the terminology employed the result of one study may then be reasonably compared with those of another The grading in the coronary arteries may take into consideration egments of steno i mean or maximum diminution in lumen size the extent of surface involvement and the types of lesions present If one excludes flat lipid streak there is considerable evi dence which indicates that the mean luminal diameter relates closely to the extent of urface area involvement In a study at the Albany Ho pital under the au pices of the Albany Medical School and the New York State Department of Health it has been found that the curves for mean wall thickne s and mall lumen size parallel each other very clo ely Al o each measurement bore a imilar relationship to the inci dence of myocardial infarcts in both exes It i generally agreed that if either *the degree of urface area of* involvement of the oronary arteries or the maximum area of lumen reduction is u ed a a method of grading the end results hould be imilar There has been needl s concern over the number of individual who may have i olated egmental occlusive plaques in the coronary artery tree in the al ence of any ignificant degree of more wide pread athero clerotic involvement This occurs usually in young individual is uncommon and is often found in associa tion with an anomalous coronary arterial circulation or underlying inflam matory lesions of the ve sel wall The e occasional cases cannot materially in fluence the findings in any large scale autopsy studie Grading may be in terms of moderate or severe in terms of pluses or in percentage but these must always refer back to clearly defined limits or categories

In the recording sy tem the di tribu tion and extent of the different types of lesions hould be indicated wherever po ible As for the aorta the degree of urface area involvement should always be recorded with attention given to the distribution and relative propor tion of the variou types of lesions

Thrombi and Intimal Hemorrhages

There is a problem at times of differ entiating organized thrombi in the coronary arterie from athero clerotic plaque For recent thrombi this i relatively simple For remote and or ganized thrombi this i difficult and in many in tances not po ible Canaliza tion of the lesion was considered as po ible evidence in favor of an old organized thrombus as oppo ed to an athero clerotic plaque but this is by no means conclu ive However such errors that would ari e in the grading and cla sification of le ions relative to thi difficulty should not ignificantly influ ence the validity of the finding Mo t *evidence indicates that the more ex* treme and older coronary athero clerotic le ions are associated more frequently with uperimpo ed thrombi (ee Table 2)

The gross recognition and recording of intimal or intramural hemorrhage a a routine in any large scale autop y tudy can erve no meaningful purpo e and may lead to erroneous conclu ion Proper tudy of intimal hemorrhages re

Table 2—Frequency at Various Age Levels of Recent Thrombi in Sudden Death in White Males with Advanced Coronary Atherosclerosis (377 Autopsied Cases)

	Age in Years			
	Under 39	40-49	50-59	60-69
Number of cases with advanced coronary atherosclerosis (total)	46	116	1[illegible]6	89
Number of cases with recent superimposed thrombi	5 (11%)	26 (2[illegible]%)	30 ([illegible])	25 (29%)

(Spain, D. M., and Bradess, V. Unpublished data from Westchester Medical Examiner Coronary Study.)

quires meticulous attention to detail with serial microscopic sectioning, clearing technic, and so forth. These procedures can generally not be performed with the minimal methodology available for large-scale studies. This view is in no way meant to underestimate the desirability and potential significance of studying the problem of intimal hemorrhages. This might very well be performed as a special investigation within a limited segment of an over-all larger study.

Other Technics

Microscopic studies do not contribute enough additional information to significantly improve the exactness of the grading process to be required as a routine procedure. Such technics that determine elasticity, viscosity of the vessel wall, as well as detailed chemical contents of the lesions do not appear to enhance the accuracy of the grading procedure.

The value of an index system of grading which arbitrarily preassigns certain values to the quality of the lesions, to the extent of the involvement, etc., is open to question. Such index systems have been developed in comparing the degree of atherosclerosis in one population group of autopsies with that of another. It was the consensus of this group that such an index system which arbitrarily assigns values to certain aspects of the lesions is biologically unsound and may lead to errors. The state of our present knowledge of atherosclerosis does not as yet permit such quantitation.

Injection technics involving the introduction of radio-opaque material into the coronary arteries or the utilization of plastic cast technics are of considerable importance for studies designed to investigate the development of collateral circulation in the coronary arterial tree. These technics, however, are unnecessary and too detailed to be performed routinely in the studies under consideration. The utilization of such technic in order to gain information on the relationship between physical activity, coronary atherosclerosis, age, and collateral circulation is important and should be encouraged.

The Heart

In order to properly evaluate the significance of the atherosclerotic lesion in the aorta and coronary arteries, it is essential that certain minimal findings in the heart be determined. The condition of the valves and pericardium should be routinely recorded so that proper evaluation may be given to the factors that contribute to any increase

in the weight of the heart. The heart should be weighed with at the most only the ascending portion of the arch of the aorta attached. It is not necessary to determine or record right and left ventricular wall thickness since such errors as the inclusion of epicardial fat or papillary muscle in the measurement and the possibility of measuring tangential cuts as well as variations in *wall thickness at different levels* would render comparison of results almost meaningless.

The heart may be opened and examined in the usually accepted manner whereby the course of the blood is followed and the septum is split up from the apex to the base. Preservation and proper examination of the coronary artery prevents a cross sectional slicing technic of the myocardium from being utilized.

The presence of all recent infarcts should be recorded and should include a statement as to their size, location and age. The classically recognized textbook description of myocardial infarction furnishes the criteria for recent infarct. Any grossly visible scar should be recorded. In the absence of any other obvious cause for such a scar and in the presence of advanced coronary atherosclerosis, this may be regarded as a healed infarct. Microscopic confirmation of recent and old infarcts is desirable but not always essential. The condition of the coronary ostia should be noted.

Information on Autopsy Record

All autopsy records should include the age, sex, race and if possible to authenticate, the country of birth, country of residence, duration of this residence, ethnic origin, and occupational history. The immediate causes of death as well as the basic or underlying disease process or cause of death should be recorded. Height and weight should be determined and wherever feasible the weight should be actually measured and not estimated. If the weight is estimated it should be so stated. Panniculus thickness should be measured in the midline midway between the xiphoid and the umbilicus.

Another method for increasing the accuracy and completeness of hospital records for the purpose of correlating certain finding with those at the autopsy is to send trained personnel into the home of the deceased within several weeks after the death and obtain information from close relatives about smoking, exercise, diet and other living habits. In the Albany study this has yielded significant information and has given more meaning to the pathological findings.

Hypertension and Diabetes Mellitus

Autopsy verification of the previous existence of hypertension and/or diabetes mellitus would be highly desirable. Unfortunately there are no certain morphologic findings for both conditions—positive or negative—to prove that these did not exist. The presence of definite myocardial hypertrophy (predominantly of the left ventricle) the absence of any other cause for this hypertrophy in combination with arteriolar change, particularly of the kidney, is strongly suggestive evidence that hypertension was present at some time during life. The presence of intercapillary glomerulosclerosis is strong evidence that diabetes mellitus was present.

Standardized Post Mortem Examination as an Integral Part of Longitudinal Epidemiologic Studies*

A review of the various project designs of the epidemiologic studies a

* Dawber, T. R. (Ed.) Report of the Conference on Longitudinal Cardiovascular Studies at the Hotel Beaconsfield, Brookline, Mass. (June 17-18) 1957.

described in the conference at Brookline in 1957 revealed that none of these studies had included any mechanism for the gathering of standardized autopsy material. This appears to be a serious deficiency. Any procedures whereby standardized post-mortem data are collected on both sudden and hospital death of individuals on whom information has been obtained over many years in such studies can enhance the value of such investigation. It would seem to be rather simple to arrange for the pathologists in the involved community to set up minimal standards to obtain the necessary information relative to cardiovascular disease.

Unexpected Unexplained Sudden or Instantaneous Death

In the absence of adequate clinical laboratory or post-mortem findings the use of unexplained sudden death as evidence of coronary atherosclerosis with ischemic myocardial disease is at present generally not acceptable. The criteria for the classification of cases as those of sudden death varies considerably in different areas. Refinement of the definition of sudden deaths to include only those cases in whom there has been an eye-witness account and in whom the unexplained or unexpected sudden deaths have occurred within a matter of minutes is desirable. This group of cases should be clearly separated from those in whom the fatal event took a longer time and from those where the individuals were found dead with no witnesses available as to the exact circumstances and their duration.

In various parts of the world depending upon the general health and disease panorama of that area the proportion of cases of sudden death that may be attributed to ischemic myocardial disease may vary. In this country it is highly possible that when the proper age, sex, and race factors are taken into consideration a considerable proportion of the cases of unexpected instantaneous death where eye-witnesses were available may be ascribed to cardiovascular disease. Before utilizing this category as evidence for ischemic myocardial disease in epidemiological studies more exact information should be obtained. A highly desirable project would be to set up a cooperative study among medical examiners offices for the purpose of determining the proportion of unexplained instantaneous death that are due to coronary atherosclerosis and ischemic myocardial disease. Such a study should be relatively simple to arrange.

Biostatistical Evaluation

It is recognized that the value of any morphologic study, no matter how meticulous the method of grading, depends for the stated purposes upon the ability to relate the autopsy findings to the population group from which the autopsies are obtained. Information must also be available concerning the characteristics of those individuals from this same population group who are not represented in the autopsy series. Careful biostatistical evaluation and design is therefore essential and should be part of every such study. The fact that previous statistical studies have pointed to dangers in drawing conclusions from hospital autopsy studies does not preclude the proper utilization of such material for the advancement of knowledge in this field.

It is the belief of this committee that with these minimal methods of studying autopsy populations a significant contribution toward a solution of the problems concerning the pathogenesis of atherosclerosis could be made. There is still no substitute in the understanding and solution of human disease for primary accurate observation in the human laboratory itself.

APPENDIX A

Definit on of Terms

(Fr m J P Stron, from Proto ol of Latin American Project)

Fatty Streak Any intimal lesion that is stained distinctly by Sudan IV and that does not how any oth r type of chan e underlying

Fibrou Plaque Any firm elevated intimal le on wh ch in th fr h state is pal grey gli tening and tran luc t After staini g it may b partially or complet ly cover d by sudanoph l c d po its If a lesion con tain a y h morrha thromb is ul ra tion or calcificat n it will be cla ified under tho e cate ories and not as a fibrous plaqu

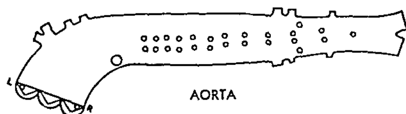
C mpl cate l Le ion Tho e areas in wh h there i hemorrha e ulceration necro or overlyin, thrombosis

Calcifi ation Areas in whi h there is calc um depo ition detectable eith r vi ually or by palpation without overlyin, hemo rha, ul rat on or thrombosi

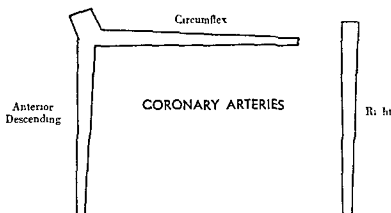
APPENDIX B 1

Preliminary Protocol of Latin American Project McGill H C and Strong J P et al

Necropsy No ______________________ Accession No ______________________



	Total Area Involved	Per cent of Involved Surface Composed of			
		Fatty Streaks	Fibrous Plaques	Hemorrhage Thrombosis Ulceration	Calcification
Descending Thoracic					
Abdominal					
Total					



	Total Area Involved	Per cent of Involved Surface Composed of			
		Fatty Streaks	Fibrous Plaques	Hemorrhage Thrombosis Ulceration	Calcification
Right					
Left Circumflex					
Left Anterior Descending					
Total					

APPENDIX B 2

Comparative Atl eroselero Study

Laboratory ______________________ Acce sion No ______________

Hospital ______________________ Necropsy No ______________

Name ____

Age ________ yrs Sex M/F Race ____________ O cupat on ______________

Country of birth ________ x ____ yrs   C ntry of re 1 nce at t me of death ________ x ____ yrs

Princ pal Fin l Diagnoses

Primary disea e ____

Immediate cau e of death ____

Other dia noses ____

____

____

State of Nutrit on
- () unknown
- () severely obese
- () moderately ob se
- () average o normal
- () thin
- () malnourished

We ght ________ k s / lbs

Length ________ cms

Th ckness of subcutaneous fat

________ cms

(m d y b ph ld d mb l

Code for principal di no is ________

Dis ea es po bly nfluenc ng athe osclerosis

\+ — ?

1 () () () hypertension established
2 () () () hypertens on presumptive
3 () () () arteriolar nephrosclero is b n n
4 () () () arteriolar neph osclero i mal na t
5 () () () pyelonephr tis acute
6 () () () pyelonephritis chronic
7 () () () glom ruloneph ti acute
8 () () () glomerul nephritis hron c
9 () () () chron c r al d sease unclas ifi d
10 () () () d abetes m ll tus, e tabl hed
11 () () () diabetes mell tus presumpt ve
1 () () () ch onic al ol ol sm
13 () () () portal c rrh si
14 () () () b liary cirrh is
15 () () () rheumatic heart disea e
16 () () () syphil ti heart disease
17 () () () hypothyro d m
18 () () () hyperthyro d m
19 () () () other end c inopath e

D seases presumably due to atherosclero is

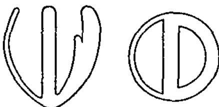
\+ — ?

1 () () () angina pectoris
2 () () () coronary occlus on
3 () () () myocardial infarction
4 () () () cerebral thrombosis
5 () () () cerebral hemorrhage
6 () () () disabling peripheral ath rosclero s
() () () mesenteric o clu on
8 () () () aort o clu on
9 () () () aortic a urysm
10 () () () art rial neph osclero i
11 () () () other un la sified

____

Heart

We ht ________ gms





APPENDIX C

From the Westchester County Medical Examiner Coronary Artery Study Spain D M and Bradess V A

Case No Sex Race M E No Ethnic Date
Age Height
Weight
Somatotype
Panniculus

Immediate Cause of Death
Circumstances

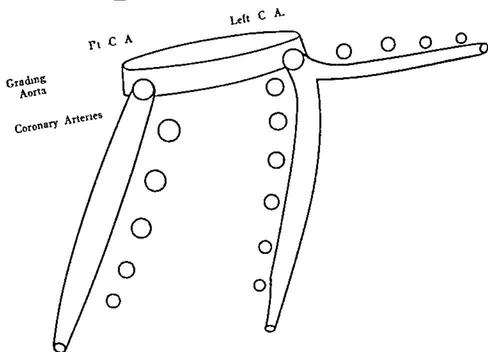
Basic Cause of Death

Occupational History

Lipid Streak
Plaque
Calcification
Thrombus

AORTA

Heart
Weight
Valves
Pericardium
Ostia
Infarcts
Location
Size
Age



COMMITTEE ON DIET, PHYSICAL ACTIVITY AND BIOCHEMICAL MEASUREMENTS

James Hundley M.D. Chairman

DIETARY intake and the expenditure of energy through physical activity are two components of the nutrition balance sheet of an individual or of a group of people. Methods of measuring dietary intake and energy expenditure are the subject of reports of two subcommittees.

Biochemical measurements are important in the analysis of dietary intake in the analysis of the relationship of physical activity to cardiovascular diseases and in diagnostic studies in general. The uses and standardization of biochemical measurements are considered by a third subcommittee.

SUBCOMMITTEE ON METHODOLOGY FOR DIET APPRAISAL

Martha Trulson Sc.D. F.A.P.H.A. Chairman

Introduction

DIETARY surveys growing out of a suspected relationship between diet and and atherogenesis have increasingly become an integral part of the design of cardiovascular epidemiological studies. The Subcommittee on Methodology for Diet Appraisal was established to examine the existing procedures for collecting and processing food intake information to study the deficiencies in current procedures and to make recommendations for future research.

The methodology considered in this report is limited to the study of food consumption of individuals rather than for an average for groups of people. Thus problems of obtaining and processing information at the family or national level are not included. Discussions of computations and laboratory *determinations will relate only to caloric* values protein content and fat content.

After a discussion and summary of the problems encountered in the collection and processing of individual food data, a second portion of the report will *present several recommendations aimed* at improving and clarifying the status of dietary surveys in relation to epidemiological studies.

Methods in Common Use in Dietary Surveys

There are several different dietary study methods in current use in epi

demiological survey. In order to yield meaningful information, they must all include certain minimal facts about the subject, such as age, sex, occupation, height, present weight, weight changes over a period of years, activity, health status (including intestinal parasitic infestation in subjects from certain areas), the usual number and time of daily meals and where the meals were eaten, and current medication or dietary supplements.

The evaluation of dietary intake involves two procedures: (1) the recording of the foods eaten during the period of observation, and (2) the conversion of the intake record into units of food or nutrients.

Collecting Food Information

There are several technics in common use for preparing a food record. The outline below presents an arbitrary classification of these procedures in terms of characteristics which have important methodological implications. These characteristics are the time period covered, the timing of the recording process, and the method used to determine amounts of foods. In these terms, the method most commonly used or most reasonably considered for epidemiological studies are:

(a) Intake at specific meals recorded concurrently in terms of weights, household measures, or estimates of quantity.
(b) Intake at specific meals reported by recall in terms of estimate of quantity or frequency of occurrence of food item.
(c) Current usual intake reported either in terms of estimates of quantity of specific food or by frequency of occurrence of food items.
(d) Past changes in intake reported in terms of frequency of occurrence of food items.

When there are concurrent recordings of intake at specific meals (method (a) above), the conversion of the intake record into units of specific nutrients may be accomplished by chemical analysis of samples of the foods or by calculation from tables of food values. When the observation involves recall (methods (b), (c), (d) inclusive), nutrient values can be estimated only through *the food value table*.

The concurrent dietary data can be recorded by the subject, by the person responsible for the subject's food, or by a trained observer. Although the recall method, utilizing either an interviewer or a self-administered questionnaire, is one of the most convenient methods of obtaining such data, it has its limitations. For example, whereas a diary or record will yield factual data, an interview will yield only the subjective average of an individual's recalled *food intake*. *This is subject to a* large human error factor—perhaps the most important variable and certainly the most difficult to estimate.

This error may be minimized by enlisting the subject's fullest cooperation and also by the skill and talents of the interviewer. The interviewer must be well trained in methods of collecting and treating data. He must be able to establish rapport with the subject. He must have knowledge of the cultural and socioeconomic factors operating in the community and speak the language or have a very competent interpreter. He must develop technics of eliciting dietary information and of assembling this information. If the subjects are to fill out questionnaires by themselves, then the questionnaire must be pretested under conditions comparable to those of the survey area.

The stress or apprehension caused by the survey itself may bring about a change in the subject's dietary practices. He may temporarily alter his intake to conform to his conception of what he should be eating. If the subject is receiving public financial assistance, he may report fewer or different foods than he normally eats because of fear that the stipend will be reduced. In

other situations the subject may eat better than he usually does to impress the workers

Arteriosclerotic heart disease and hypertension develop over a period of years Ideally the entire past history of nutritional and other environmental factors should be assessed The value of dietary studies of individuals actual current intakes for short periods—one day one week or one month—is questionable unless it can be established that the short term studies reflect usual eating patterns of the past

Review of Literature

Studies of daily food intake have revealed marked variations even in the same individual[1-3] Yudkin[4] using the daily records of postgraduate dietetic students at King's College designed a study to provide data on the adequacy of dietary studies taken for periods of less than seven days He found that caloric intake of an individual can differ by as much as 68 per cent from week to week his data showed that the fat intake was largely responsible for this variation Thompson[5] weighed the daily food intakes of a group of pregnant women and reported that the profiles for the nutrient content of the individual diet appeared to retain its main characteristics in two widely separated weeks

Chappell[6] weighed her own food every day for more than a year She concluded that an observation period longer than one week has little advantage over shorter ones if only an average estimate of nutrients is desired A more accurate estimate could be obtained from three weekly records of weighing chosen seasonally throughout the year McHenry[7] after studying the food intakes of a small group of normal persons at intervals throughout a year reported that the variations were of such magnitude that if the intakes for this group had been recorded for a single week's period the results would have varied considerably depending upon which week was used

Young and co-workers[8] concluded that when daily diaries are used averages for groups did not appear to vary sufficiently from week to week to warrant more than a seven day record In contrast to adequately study the intake of an individual it would appear that for some individuals more than a single week's record would be desirable

Variations in the dietary intake depend upon many factors especially food supply seasonal change and socioeconomic factors Religious and cultural patterns alter intakes of certain foods at specific periods of the year The degree of internal variability and its relationship to the design of the total study must be considered in selecting the time span over which the dietary information will be collected

Estimates of nutrient intakes calculated from the food table vary with the method of collection of information on food intake even when the same individuals and the same food intakes are being studied Experience in comparing nutrient values resulting from three different methods of collecting data are summarized by Young[9] as follows

1 *The dietary history [defined by Burke as* the average food intake over a considerable period [10]] was compared with the 24-hour recall and the seven day record with 24-hour recall, as methods of estimating the nutrient intake of an individual and of a group Data for these comparisons were obtained from three different population groups grade school children (New York) high school and college students (Rhode Island) and pregnant women (Massachusetts)
2 For an individual in any of the three population groups studied the 24-hour recall did not give the same estimate of dietary intake as the dietary history
3 For an individual in any of the three population groups studied, the 24-hour recall did not give the same estimate of dietary intake as the seven day record To describe the intake of individuals th

two methods could not be used interchangeably

4 For the mean of a group the dietary history gave distinctively higher values for grade school children and for pregnant women than did the estimates obtained by a 24-hour recall The history and 24-hour recall gave results which were in better agreement for the college group studied.

5 For the mean of a group the seven day record and the 24-hour recall tended to give approximately the same estimates for the dietary intake for most nutrients. This was true for all three population groups to which the two methods were applied grade school high school and college students and pregnant women Under certain circumstances the 24-hour recall can be substituted for the seven day record in estimating group intakes.

Bransby[1] also reported that the values calculated from weighing household measurements and questioning of the children were in broad agreement for energy and nutrient content These did not check closely with chemical analyses of the foods (Tables 1 2)

Morrison[11] found that the memories of eight scientists for a 24 hour recall of food intake were extremely un ati

Table 1—Average Daily Energy and Nutrient Intakes Found by Four Methods of Survey in the National Children s Home Harpenden (49 Children)

Method of Survey

Item	Weighing Value	Weighing S D *	Homely Measures Value	Homely Measures S D *	Questioning Value	Questioning S D *	Chemical Analysis Value	Chemical Analysis S D *
Calories	2 660	507	2 71	423	2 601	487	2 381	218
Protein gm†	83	18	89	16	81	18	89	16
Fat gm	96	22	107	21	95	19	81	14
CHO gm‡	366	69	363	52	351	68	324	59

* These are standard deviations for a single child and were calculated from the actual three day intakes of nutrients the resulting values being divided by three to obtain the above figures.
† Protein—N x 6 0 as the diets contain both animal and cereal protein
‡ The starch values determined by the method adopted were increased by 21 per cent to permit comparison between analytical and calculated results.

Adapted from Bransby E R Daubney C G and King J Comparison of Results Obtained by Different Methods of Individual Dietary Survey Table 5 Brit J Nutrition 2 101 1948

Table 2—Correlation Coefficients Between Energy and Nutrient Values Found by Four Methods of Dietary Survey in the National Children s Home Harpenden

Methods Correlated	Calories	Protein	Fat	Carbohydrate
W x H	0 94	0 90	0 93	0 93
W x Q	0 94	0 94	0 91	0 93
W x A	0 87	0 92	0.57	0 81
H x Q	0 91	0 87	0 87	0 91
H x A	0 85	0 8_	0 53	0 71
Q x A	0 80	0 88	0 43	0 75

* W=Weighing Q=Questioning H=Homely measures A=Chemical analysis

Adapted from Bransby E R Daubney C G and King J Comparison of Results Obtained by Different Methods of Individual Dietary Survey Table 8 Brit. J Nutrition 2 103 1948

factory on an individual ba i How ever the averages for the group were similar to the calculated averages of the weighed food

There is i paucity of published data on methods of tudying long range eat ing pattern Trul on and McCann[1] in ve tigated the patterns of 39 Italian American male factory workers using a research history method and repeated the study after a two year interval The mean intakes of the group for calories protein and fat as estimated from the two surveys did not differ significantly but there was considerable individual variation The correlation coefficients between the two urveys for the intake of protein fat and carbohydrate were approximately 0 5 The error in the method and changes in food supplies economic status occupation etc could have *contributed to these differences* The information collected may be a closer approximation of current eating practices than it is of long range pat tern

Marr[13] examined the dietary records of middle aged male British bank officers obtained by the weighing of food for two periods The second period was selected approximately ix months after the first period in an attempt to mea ure seasonal variations as well as reliability of reporting The data from 25 men are reported in Table 3 There appears to be considerable stability in the nutri tional habits of these men during this six month period For energy value and for the nutrients calculated (protein and fat) correlation coefficients for the two period ranged from 0 72 to 0 87 The co fficients for fat (land animal marine animal and vegetable) ranged from 0 81 to 0 87 (Table 3)

From the preceding di cussion it is evident that more knowledge is needed regarding the reliability of the results obtained by different methods in com mon use for collecting dietary informa tion It is not yet pos ible to utilize intake results obtained by one method for predicting results expected from *another method* *Further re earch* is needed on individual food consumption to identify the characteri tics of a diet pattern which are con tant and not greatly affected by daily and weekly variation

The problems encountered in the proc e sing of dietary data will be presented and discu ed in the next portion of this report

Table 3—Twenty f ve Ind idual Repeat Weeks Weighed Diet Survey

(Bank officers males 40-55 years inclusive)

	1957–1958 A erage Daily Consumption		
	First Survey	*Second Survey*	Correlation Coeffic ent
Calories (Cal)	? ,69	-819	0 84
Protein (gm)	8?	83	0 7-
Carbohydrate (gm)	3 6	338	0 8?
Fat total (gm)	1?7	1?6	0 85
an mal (gm)	93	92	0 80
marine (gm)	6	7	0 81
veg table (gm)	?8	27	0 87
Calories from fat (%)	41	40	0 83

Marr J W Heady J A and Morr s J N Repeat Indi dual We ghed Diet Surveys Proc Nutr tion S ciety 18 1 xi 1959

Table 4—Calculated Intakes of Food Cc mponents Comparison of Analysis of Duplicate Samples of Diets and Calculation of The r Contents

Nutrient	Method	Day 1	2	3	4	5	6	7
Energy	Analy is							
(calories)	Sample a		1,968	2 29,	2 512	2 018	2 051	2,384
	Sample b	1,521	1 941	2,27,	2 553	2 0,5	2,032	2 411
	Difference		27	20	41	57	19	27
	Estimation	1,516	2 152	2,260	2 6 4	2,238	2,288	2,339
Protein	Analysi							
(gm)	Sample a	56.5	16 0	64 4	87 0	68 0	74 4	86 2
	Sampl b	53 8	69 7	67 6	85.5	72.8	76 0	85 7
	Differen e	2 7	6.3	3 2	1 5	4 8	1 6	0.5
	F timation†	65 6	95 9	56	84.5	84 1	83 7	83 6

Heat of combu tion

† Values derived from standard tables by multiplying total intakes of protein fat and carbohydrate by factors 5 65 9 45 and 4 1 respectively

Thomas R. U et al Nutritional Status of Children. XIII Accuracy of Calculat d Intakes of Food Compon nt with Respect to Analytical Values. J Am Dietet. A 26 11 891 1950

Processing Dietary Data

There are three method which the re earcher may u e to evaluate the dietary data (a) chemical analysis of representative amples of the food con umed (b) calculation of individual nutrient using food tables and (c) classification of information according to food usage Each of these method will be examined briefly

Laborato y Analys s

Acceptable methods have been tand ardized for the analy is of food for a few nutrients Procedures for pyridox ine determinations remain unsatis factory Analy is of food for total fat continues to present problems while the be t method for analy is for pecific fatty acid remain to be selected

Work on these problems continues currently in the U S Department of Agriculture as well as in many other laboratories A committee appointed by the Interdepartmental Committee on Nutrition for National Defen e is work ing on further tandardization of methods suitable for obtaining valid aliquots and for the analysis of food samples

Table 4 hows differences in the analy is of duplicate amples a reported by Thoma [14] Difficulties were de cribed in obtaining consistent results from the analysis of duplicate ample from nonhomogeneous dishes uch a meat stew The greate t variation oc curred when uch foods as fried pota toes or green beans cooked with bacon fat were on the menu

The be t data on nutrient intake for a specific time segment are probably ob tained by weighing and analyzing food items or aliquots of the diet as eaten Expen e and practicality may make uch detailed observations infea ible This technic has the further limitation that it can be u ed only for pro pective studies which cover a pecific time pan and require concurrent observation As with other methods the po ibility exi ts that weighing and sampling may influence the kinds and amounts of food the subject eats by focu ing his atten tion on his diet

The main usefulness of direct analysis of foods in epidemiological studies is for establishing the reliability of results obtained from other methods

Calculation from Food Tables

Dietary intake obtained by recall technics and meal recordings are frequently converted to nutrient intake by use of the standard food tables

There are a number of studies in the literature which compare chemical analysis to calculated reports Table 5 presents a summary of the differences resulting from treatment of the same dietary data by both laboratory analysis and calculation from food tables[11-44] Caloric and protein values were within 10 per cent in more than half the cases *but only 25 per cent of the fat determinations* were within this range Only 15 per cent of the calculated values for calories and protein varied *from laboratory analysis figures by more* than 20 per cent while more than 50 per cent of the fat determinations were outside this range

Most of these differences can be attributed to the calculation of the protein and fat content of the meat Tables of food composition prior to 1950 and some of the more recent tables express the values for raw meats on the basis of carcass or wholesale cuts and have little or no information on trimmed retail cuts either raw or cooked It has been customary to use the data for the raw meat in estimating nutritive values When meat is cooked there is considerable loss of fat into the drippings resulting in a large reduction in calories and very little loss in protein Fat adhering to the muscle frequently is trimmed from the meat after it is *cooked thereby reducing the calories* further Therefore it is to be expected that the values for meat as calculated from the tables will be high for fat and consequently for calories but will *be within a reasonable range for pro*tein If meat constitutes a large proportion of the diet the calculated values for fat and calories for the diet as a whole *probably also will be too high*

A recent publication[44] concerning the nutritive value of cooked meat helps to elucidate some of the apparent discrepancies between analysis and calculation of meat fat Future revision of food tables are planned to provide more

Table 5—Comparison of Calculations from Food Tables with Chemical Analyses

Per cent Difference—Calculation vs Chemical Analysis

	−30 or More	−20 to −29.9	−10 to −19.9	±9.9	+10 to +19.9	+20 to +29.9	+30 or More	Total
Calories								
No of cases	0	8	29	218	73	28	22	378
% of cases	0	2.1	7.7	57.7	19.3	7.4	5.8	100.0
Fat								
No of cases	20	10	36	66	24	35	68	259
% of cases	7.7	3.8	13.9	25.5	9.3	13.5	26.3	100.0
Protein								
No of cases	13	14	0	170	29	14	8	318
% of cases	4.1	4.4	21	53.5	9.1	4.4	2.4	100.0

Based on 29 studies Two of the studies are Canadian four are British and the remainder are American *There are 23 different studies reporting comparisons of calories, 25 of protein* and 21 of fat. These studies were published from 1937 to 1959 See references 1 5 and 15 to 44

Table 6—Calculations of the Same Weighed Diets by Workers in Eight Different States—Based on 21 One-Day Diet Records

Means and Standard Deviations for Calories and Protein

	Mo	Wis	Iowa	Ill.	Mich	Minn	S D (a)	S D (b)
Calories								
Mean	1,978	1,820	1,872	1,893	1,875	1,936	1,924	1,904
S d *	432	329	387	351	417	390	406	398
Range	1,295	1,026	1,410	1,233	1,711	1,388	1,567	1,616
Protein (gm)								
Mean	65.6	61.9	57.2	70.9	61.9	55.9	62.4	57.2
S d.	17.2	15.9	15.4	33.1	15.5	15.3	15.9	16.9
Range	68.9	65.9	68.7	157.8	67.3	61.7	68.1	74.8

* Standard deviation

Unpublished data furnished by Dr Wilma Brewer based on a pilot study conducted by the NC 5 Tech Committee compilation of data by Harriet Roberts

detailed descriptions of cooked meat *Accuracy of calculations will depend* to a large extent on adequate description of a food item as it is actually eaten

It is recognized that direct chemical analysis is the best available method for determining the exact amounts of nutrients supplied by a particular food sample at a particular time However calculations using the best available tables of food composition when applied to a detailed food record compiled over a long period of time may *be more representative of usual intake* than chemical analysis of samples of foods eaten during a short period

In this connection reference is made to the background of the figures on nutritive value of foods published by the Department of Agriculture The values shown in these tables of food composition are not necessarily arithmetical averages of all analyses available for each nutrient in each food Many factors are taken into consideration in deriving the particular value shown such as variety seasonal and geographic differences production and consumption statistics shortage and manufacturing and preparation practices The nutrient values in the table *represent average values throughout the year*

The use of food tables for determining nutrient content of mixed dishes requires very special care since recipes will differ from day to day from house to house and from region to region Unpublished data from a pilot study[16] show wide variations in the calculation of nutrient content by eight different nutritionists using the same weighed diets and food tables (Table 6) The lack of adequate description of food *mixtures places an added burden on the* calculator s judgment in selecting the appropriate item in the food table

Calculation of the nutritive value of carefully obtained food records from appropriate food tables has many advantages The researcher has great latitude in selecting the specific components to be calculated The only limitation is the data in food tables With improvements in food tables the opportunities to search for possible interrelationships between different components of the food intake and other aspects of the subject s condition will be greatly extended

Food Usage

The third method of processing the dietary material is according to food usage. Classification according to the frequency of use, amount, type of preparation, periodic intervals of feasting or fasting, patterns of alcohol consumption and use of condiments may help describe the subject's nutritional environment. A regional publication of the U. S. Department of Agriculture[16] describes homemakers' meals (Table 7). Caloric and protein intake for the Birmingham and Minneapolis women were in close agreement. However, when the diets were classified according to food groups, considerable differences were observed.

No attempt has been made here to review the literature, but results from this and similar reports suggest that further study and experimentation with the raw data, in this case intake in terms of food items, may suggest important relationships between food intake and cardiovascular disease.

Discussion

A major defect in the collection and processing of dietary data lies in our inability to make precise or even approximate statements concerning the reliability of the various procedures in current usage. Until such information is available, it is difficult to evaluate the usefulness of dietary appraisal in epidemiological studies.

Mechanical inaccuracies can be decreased through greater use of automatic devices for the processing of data, while variations due to subjective judgments will be reduced to measurable proportions only through standardization of each procedure.

For every dietary study, consideration should be given to establishing the degree of reliability for each step in the

Table 7—One Day Food Intake of Homemakers

Average nutrient content	Birmingham (261 Subjects)	Minneapolis (245 Subjects)
Calories	1,8[illegible]0	1 720
Protein (gm)	57	61

Food intake according to food groups
Per cent calories contributed by 11 food groups

	Birmingham ([illegible]61 Subjects)	Minneapolis (245 Subjects)
	Per cent	Per cent
Milk, cream, ice cream and cheese	9 6	14.3
Fats, oils	[illegible]3 3	10
Eggs	3 2	2.8
Meat, poultry and fish	16 9	21 4
Dry beans, peas and nuts	3 4	1.2
Potatoes and sweet potatoes	4 1	4 2
Citrus fruit and tomato	1 6	2.8
Leafy, green and yellow vegetables	1.5	1.6
Other vegetables and fruits	3 4	6 4
Sugars and other sweets	9 2	6 1
Grain products	23 8	[illegible]9 0

Adapted from Clark, F., and Fincher, L. J. Nutritive Content of Homemakers' Meals, Four Cities, Winter 1948. USDA Agricultural Information Bull. No. 112 (Mar.) 1954, pp. 3 and 30.

collection and processing of dietary information. Such testing of the reproducibility of results should begin with a demonstration of the dependability of the instrument and procedures selected for obtaining and for processing the information. Equally important will be the reliability of the subject as an informant. He should be able to report repeatedly the same factual information. The interviewer must have the ability to interpret diet information objectively. For each procedure which depends upon a subjective interpretation, results from two or more workers should be compared. Through repeated interviews with the same subject and through the use of *built in cross checks in a questionnaire*, procedures can be pretested for a selected sample prior to the survey of the total population to be studied. Attention to the areas for which reliability is poor or for which reliability appears difficult to check will more clearly point out the deficiencies in presently employed methods.

In addition to the reliability, that is the error variation in methods of collecting and processing dietary data, the validity of a method is an important criterion of its usefulness. The validity of the method will be judged by the extent to which the data it yield are a true measure of what the investigator wishes to describe. In other words, do the data obtained answer the question that is asked or satisfy the purpose of the investigator? The primary problem is to evaluate how accurately any method of collecting information measures dietary intake, keeping in mind that reliable data for a specific period such as a week or two may not be a valid measure of the characteristic diet of an individual.

Summary

The principles of dietary studies currently *in use in epidemiological investigations* of cardiovascular disease are described in the main body of the report.

There is need for dietary data on individuals which can be related to other information about them. In planning dietary studies certain decisions must be made:

1. What are the objectives for the dietary study?
2. What hypothesis is under consideration?
3. What shall be the time span involved in the dietary study?
   - (a) Intake for a specific time
   - (b) Usual characteristic intake for some defined period
   - (c) Combinations of these
4. What methods shall be used for collecting data?
   - (a) Record
   - (b) Recall
   - (c) Composite of duplicate meals
5. How will amounts be reported?
   - (a) Weighing
   - (b) Measuring
   - (c) Estimating
6. Who shall be the informant?
   - (a) Subject himself
   - (b) Person responsible for the subject's food
   - (c) Both (a) and (b)
   - (d) Observer
7. Who will record the information or sample and collect the food?
   - (a) The informant
   - (b) A trained interviewer
   - (c) (1) A nutritionist or other professional person in food or nutrition or closely related field
     (2) Other persons knowledgeable about food
8. How certain is the investigator that his method is securing the information desired?
   - (a) The schedule must be pretested unless it has been tested under similar conditions
   - (b) Interviewers should undergo a thorough training period which includes actual collection and treatment of data in trial situation and information on the cultural and socioeconomic factors operating in the community
9. What additional information concerning the subject is needed?
   - (a) Certain minimal basic facts about the subject must be known: age, sex, physical activity and data on physical measurements and present and

past health s atus that are to be studie l in relation to the dietary data Some social and econom c data may also b u eful

10 How can the data be proces ed?
   (a) Chem cal analysis of f od composites or ind v dual foods
   (b) Computation of energy value and nu trient f om tables of food compo i tion
   (c) Cla ification accord g to food usa or patterns

11 What information can l e obtain d f om the dietary intake?
   (a) The investigator may search for p sible terrelat onships between differ ent components of the f o l intake and between the food intake and nutritional health or oth r a pect of the subje t s condition

12 What ar the gaps or l cks in method ology?
   (a) Lacks or lim tation ha e been discussed in the main body of the pape and the following recommenda tions to h lp imp ove m ethodology for diet appra sal have b en mad by the committee

Recommendations

The members of the committe recog nize that ways mu t be developed to minimize current problems noted in the present methodology of ecuring infor mation on food con umption of indi viduals for u e in epidemiological tudies of cardiovascular disease They make the following recommendation

A *Assembling of Published and Un published Work Relating to Method ology of Diet Appraisal*

The committee recommend that a collection compilation and critical evaluation be made of publi hed and unpublished work relating to meth odology for diet apprai al particularly material on validation and reliability of methods currently being u ed It is recommended that uch an evaluation be publi hed and be made available to workers in the field of epidemiological tudies of cardiova cular di ea e

B *Preservation of the Original Dietary Data*

The committee sugge ts that a means of pre ervation of dietary data be ex plored Government agencies can use the facilities of the National Archive For other arrangements through ap propriate journals with a repo itory uch a the Library of Congres will allow for storage and later u e With uch a y tem well collected dietary material from numerou earlier studies, reported only in terms of carbohydrate protein and calories for example could now be proce ed for other nutrients

C *Continued Study and Development of Methods of Chemical Analysis Food Composition Tables and Classification and Patterns of Food Usage*

(1) Chemical Analysis—The commit tee recommends continued research on the chemical analysis of food and the standardization of methods Analy is for fat technics of collecting and com po iting food methods of analysis of such compo ites as well as better ana lytical methods for nutrients such as fatty acids and pyridoxine may be cited as areas for inve tigation

(2) Food Tables—The committee recommends the expan ion of the tables of food compo ition currently available Activities are under way to improve and extend several of these However more information is needed concerning compo ition of recipe di hes or mixed dishe regional di hes and commer cially prepared or partly prepared ready to eat food or food mixes

One pos ibility for covering regional variations in nutrient composition of locally grown and locally con umed foods would be to have the U S Depart ment of Agriculture collect, compile and publi h uch information when avail able

(3) Cla sification of Food—It may

be as important to investigate the intake of certain foods types of food or groups of food as it is to estimate the consumption of nutrients they supply The committee recommends that additional study be devoted to this area particularly to accommodate the testing of current hypotheses in epidemiological studies of cardiovascular disease

D Processing of Dietary Data

To standardize and expedite the processing of dietary data the use of machine computation should be further explored

The committee recommends that more systematic effort be devoted to utilizing modern machine devices to calculate dietary intake information into nutrients food groups meal patterns etc This has already been done for a few studies but there is no standardized procedure The saving of time and money as well as the increase in accuracy make this most important

E Research in Methodology

(1) Sh rt Method for Obtaini g D etary Inform t on

The committee recognizes that there is need for new approaches to methods for obtaining dietary data that can be u ed in epidemiological studies Since the objective of epidemiological tudies is to search for evidence of possible association between a dependent variable (such as ischemic heart di ease) and an independent variable such a study usually is concerned with a relatively large number of persons who are to be classified into subgroups which will differentiate the persons according to the independent variable When food intake is the independent variable to be examined there are major difficulties to be overcome because unlike such variables as age hours of sleep or even number of cigarettes smoked per day food intake is a multifactor variable which can be cla sified in many different ways In any study in which diet or level of consumption of pecific commodities or nutrients is to be one of the independent variables one or more methods of classification must be decided upon and then the data collected in such a way that this classification will be practicable

If an hypothesis about the relation of a specific nutrient food or group of food to a disea e is to be tested this will determine the axis on which persons will be classified In many recent studies of ischemic heart disease association of the disease with amount and types of fat and with the percentages of total calories obtained from such sources have been of principal interest The results of such studies in the United States have not proved definite as ocia tions Con equently there is a desire to take a new look at the total problem of food intake dietary patterns eating habits etc and to correlate this with calorie balance If this is carried out with no hypothesis to guide the collection of data what steps can be taken to develop procedures for searching for evidence on which to base some hypothesis for more intensive and controlled investigation?

Es entially the problem is to find and describe the major differences among individuals with respect to foods eaten and to develop practical methods for obtaining information needed for clas ifying people according to selected dietary characteristic If groups can be clearly differentiated by use or non use high or low u e of any food item or items or other dietary characteristics then such characteristics can be tested for a sociation with the disease

It is propo ed therefore that a short, simple schedule for collecting information about types of foods used and meal patterns be prepared and used for questioning persons in several samples of selected populations The populations studied should be from communities

known to differ with respect to mortality or prevalence rates for ischemic heart disease These also might be groups with different rates within a community The objective would be to compare either mortality or prevalence rates for persons in various diet classifications

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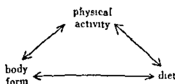
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SUBCOMMITTEE ON METHODS FOR ACQUIRING INFORMATION ON PHYSICAL ACTIVITY AND BODY FORM

Harwood S Belding Ph D Chairman

1 The Task

SUFFICIENT suggestive evidence has been collected of relationship between level of physical activity and development of cardiovascular disease to encourage a rash of hypotheses regarding the mechanisms involved Meanwhile further epidemiological studies are required better to define the relationship Such studies will continue to be complicated by interactions of physical activity with body form (constitution) and with diet It is obvious that any one of these factors may influence the other two The fact that the subject of dietary measurements is handled by another subcommittee should not be taken as indication that relationships of any one of these factors can be understood without attention to the other two



The task of this subcommittee is to consider means by which the physical activity and body form of population groups or of individuals within such groups may be assessed The consideration of hypotheses and the evaluation of evidence now available is beyond the scope of our assignment We deal here only with methods of assessment of physical activity and body form

Our approach to this problem was first to decide what it is that we should know about physical activity of a population under study then to indicate and discuss means for acquiring the information This approach was repeated in dealing with body form

2 Physical Activity

We are agreed that whether the purpose be to describe two homogeneous population groups having different activity habits or to describe individual in a population under study it is necessary to know (a) what the physical activities have been and the environ

mental conditions under which they have been conducted (i.e. what have been the stresses) and (b) what physiological demand the activities have made (i.e. what have been the strains).

A *Description of Physical Activities (The Stresses)*

(1) Average Daily Energy Expenditure

This is essential information for even the most primitive classification into activity groups, namely, relatively active and relatively sedentary. It will also be most closely tied to studies of effects of nutritional factors. Such information based on activity level in the immediate past of subjects will probably be inadequate for epidemiologic purposes. Ideally, information will be sought over the lifetime and at the least it will be needed for the adult years.

Exactness of estimate of average daily energy expenditure cannot be expected from technics applicable to epidemiological studies of long-term physiological changes. It seems likely that the general level of physical activity can only be described in terms of about three grades: light, moderate and heavy.* *For uniformity in usage of these terms* we suggest that light be used to describe daily activities involving up to 2,400 calories of energy expenditure per day for a man of average† size, moderate be used for 2,400-3,200 calories, and heavy be used for expenditures in excess of 3,200 calories. Since the energy requirement for rest is about 1,800 calories/day, light represents up to 600 calories of work, moderate up to 1,200 and heavy above 1,200. Assessment may be by interview or more accurately by study of the characteristics of the job performed and supplementary information from available sources on activities during off-job hours. Of use in these connections are summaries that have been published on the energy cost of various tasks (see Passmore, R. and Durnin, J. V. G. A.: Physiol. Rev. 35: 801-840 (Oct.) 1955). However, some *common tasks have not been studied.* Furthermore, published values may be

* It is believed that classifying workers with reasonable accuracy into three categories of physical activity requires visits to the job site by experienced observers and under ideal circumstances, measurement of the energy requirement of any tasks with which the observers are unfamiliar. It should be recognized that when such classification rests primarily on occupation, the assumption is made that leisure time activities are not so distributed that the energy expenditure of the sedentary group is increased enough to compromise the difference in energy levels between the sedentary and moderately active group. It may be noted that this was actually the case in the study of miners and clerks at Fife, Scotland, in 1953, where it was found that in 19 colliery miners the energy expenditure on activities not at work was 1,490 calories per man per day, while among 10 clerks it was 1,410 calories. Common sense classifications will place clerks in the light activity group and miners in the group which requires heavy physical activity, yet the total energy expenditure of miners was 3,660 calories and that of clerks 2,800. The difference in total energy expenditure of 860 calories is not really large and means that if one is to define a group employed in moderate physical activity one is attempting to distinguish differences of the order of only 300 or 400 calories. To do this with precision obviously requires a good deal more than just casual questioning.

When the observer does not have first-hand knowledge of actual job conditions, it is believed that a satisfactory classification of the activity level can be made by using two classes designated sedentary and physically active, with a third group designated as moderately active and/or uncertain. This kind of classification was used by Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G. and Parks, J. W.: Lancet 2: 1053-1057 (No. 21) 1953, in classifying death certificate data in activity groups based on last known occupation and by workers in the Minnesota Laboratory of Physiological Hygiene studying railroad employees.

† A man of average size, i.e., one who weighs 70 kilograms, is about 178 cm tall and has a surface area of 1.85 m². For most purposes, body weight is an adequate measure of resting energy expenditure. Its accuracy as a measure of average daily energy expenditure varies somewhat with the amount and kind of work done. The arbitrary caloric levels for grades of work may be adjusted downward or upward in accordance with percentage deviation of an individual's weight from 70 kilograms, the degree of accuracy required and the range of work energy being studied may indicate the use of more nearly precise formulae.

misleading because the energy expenditures for a particular job may not be equivalent from country to country due to differences in methods For example E H Christensen s values (Symposium on Fatigue Floyd W F and Welford A T (Ed) London H K Lewis 1953 pp 93 108) for various jobs in the Swedish steel industry do not correspond to those of Ford A B Hellerstein H K and Turrell D J (Circulation 20 537 548 (Oct) 1959) for these jobs in Cleveland

For relatively homogeneous population groups with established and consistent patterns of activity (e g prison populations or fishermen in a fleet) it would be worth while to make sample measurements of oxygen utilization and to maintain an accurate log of time spent in various activities as a means of improving the estimate of total energy utilization A little arithmetic will show that the largest errors in estimating work calories are in the estimation of time spent at any particular task Probably the most accurate index of total energy expenditure (for such populations) may be acquired by careful assessment of the caloric value of the diet

Meticulous application of existing method for estimating over all daily energy expenditure cannot be expected to have accuracy better than ± 300 calories This degree of accuracy will not be required for most epidemiologic studies

(2) Variety and Pattern of Activity

This information may be as important as that on average level of activity Relatively brief but frequent bursts of activity may be significant for establishing or maintaining muscular power and cardiovascular capacity among those classified as less active on the basis of average daily energy expenditure Furthermore man being rhythmic as regards activity level the very rhythmic pattern between work and rest may affect his long term well being

Desirable knowledge includes customary peaks of energy expenditure and their frequency The types of muscular activity also may be pertinent e g whether static or dynamic (because static heavy effort affects cardiac filling —the Valsalva effect) whether heavy or light whether involving few or many muscle groups (see Lehmann G Praktische Arbeitsphysiologie Stuttgart Georg Thieme Verlag 1953) Information on activity during and outside of gainful employment including sexual activity and sleep habits is needed for a reasonably complete picture

Methods involved in assessment of activity peaks and pattern of activity are generally similar to those utilized for determining the total daily energy expenditure The emphasis here is on determination of the history of heavy demands on the circulation and on distinguishing between situations involving free filling and restricted filling of the heart The likelihood of bias in the subject s evaluation of his maximum efforts is not known Error of estimate is encouraged by the fact that most activities (whether they be brick laying climbing hill or playing tennis) may be accomplished at widely varying speed

Data on current on and off job activities of subjects can often be quite accurate However such will not be regarded as sufficient for purposes of studies of onset of chronic disease Collection of data on the lifetime of prior activity by interview of subject relatives and associates is necessary despite the fact that such data will be less accurate

In taking a detailed activity history one must inquire carefully regarding the principal energy consuming tasks on the job and the time spent doing each one (See Appendix 2 for check list of items to be covered in ques-

tionnaires regarding phy ical activity) Attention hould al o be paid to rest pau es and activities requiring little or no energy the mode of transportation to and from work and the activities during recreational periods Question hould be directed at the amount of time spent walking both on the job and off the job Care should be taken to see that the subject does not confu e standing with walking In all cases an attempt hould be made to obtain ome estimate of the time spent in each task

Each subject should be asked to de cribe the most trenuous ta k which he performs and the frequency with which he performs it It is believed that this question should be left to the end of the interview since it is a leading que tion which sometimes leads to overstatement and boasting Under ideal circumstances then an interview would yield an estimate of the total energy expenditure in three grades plus an indication of the intensity and frequency of the significant peak loads

Again under good circumstances pecial que tioning into leisure time activities should be carried out Experience has shown that the majority of energy consuming leisure time activities are of the type which demand a low rate of energy expenditure and center around gardening home repair and hobbies requiring tools or ports such as golf (except on hilly courses) which do not require peaks of high energy expenditure However there is a group of men who spend time in gyms participating in bona fide high peak energy expenditure tasks uch as squash and handball requiring the utilization of a good deal of anaerobic energy Anaerobic exerci e of this kind is quantitatively and qualitatively different from the u ual phy ical activity of the average wage earner with or without hobbies and in those situations where it is fea ible men of this type hould be placed in a eparate category It is believed that these men are easily identified if the observer will take time to make a di tinction between men who go to the gym for companionship and only a token amount of exercise and those men who spend three to four hours a week in participation in high energy level conte ts

It should be empha ized that there has been practically no systematic effort to validate an activity history When one actually examines the available data it is found that very little is actually known regarding physical activity patterns and energy expenditures of the American wage earner living in large urban centers

Since walking is an activity which requires more energy expenditure than that found for many production workers in industry (Hellerstein H K and Ford A B J A M A 164 225 231 (May 18) 1957 Ford and Hellerstein Circulation 18 823 832 (Nov) 1958) the time pent in walking by sale men and office workers in large banks and industrial concerns is of real consequence Very little is known concerning walking patterns of such men whose work would be cla ed superficially as light, but which may actually fall into a higher category

The time di tribution of activities is important but it may be just as important to identify the man who always walks rapidly and prefers walking up stairs to riding an elevator It should be noted that increasing the peed of walking on the level from 2 0 to 4 0 miles per hour increases the calories expended per minute (but not per mile) for a man who weighs 160 pounds from 3 2 to 5 8 In this context it may be noted that there is no information on the distribution of walking peeds among American men Walking peed might be u ed as an index of drive in tudies where this was a parameter of interest

Pulse rate* and pulmonary ventilation† are correlated with the energy demands of activity If a high degree of correlation were established for such physiologic re ponses data obtained from 24 hour u e of monitoring apparatus could be converted to values for *peak and daily energy expenditure*

See Appendix 1 for ources of information on method for objective measurement of energy utilization

(3) En ronmental Factors

Certain components of the environment may enlarge or diminish the stress of activity Of mo t obvious importance is the thermal environment Work in heat is accompli hed at greater cardiac cost (e g Robin on S Turrell E S and Gerking S D Am J Physiol 143 21 31 (Jan) 1945 Pelding H S and Hatch T F Heating Piping and Air Conditioning ASHAE Journal Section 127 pp 129 136 (Aug) 1955) and with di tribution of a sub tantial fraction of output through cutaneous vessels habituation to cold involves different utilization of the cardiovascular system The general thermal environment should be a matter of record particularly if compari on i to be made between population groups from geographical areas with widely different climatic condition For subjects exposed to proce s heat in performance of their jobs the fact of exposure should be recorded

Christensen (loc cit) cla sifi s the hea i ness of work as follows

	Cal/hr	Pulse/min
unduly heavy	750	above 175
very heavy	600	150-175
heavy	450	125 150
moderately heavy	300	100-125
light	150	75 100

These values apply for the work it lf They do not includ re t pau es

† Developers of the IMP (see Appendix 1) believe that re piratory m nute volume i closely prop rt onal to energy expend ture over a wide ran e of activities The IMP y eld direct information on respiratory minute volume

Objective data on physiologic re ponses to work (vide infra) should be collected under tandardized thermal conditions if this is not fea ible the environmental conditions should be described

Other environmental factors of po ible *consequence and interest include* barometric pressure noi e and vibration

The ociologic and cultural environments in which life activities are conducted may be of importance in potentiating or canceling effect of phy ical activity per se It is hardly within our phere of competence or re pon ibility to point out methods of describin the e environments in terms of the tre es (ten ions or drives) which they present Nevertheless we recognize that ome jobs involve threat of cata trophic con equence for mi takes in judgment or performance (e g piloting a plane or other public tran portation high level decision making) and that individual workers on such jobs may or may not *be affected by these stres es depending* on temperament but the pre ence of uch tress should be a matter of record in epidemiologic studies In other instances personal drive may result from competition This may be reflected in average daily energy expenditure (pace of physical activity) but if the "drive is nervous rather than phy i cal in it expression it may not be mea urable by available methods

B Description of Physiologic Strains of Activity

(1) C stom ry Act ty

Descriptions of the work pattern and environmental conditions of a tudy population are no more important than *knowledge of the phy iologic re ponses* of the population to the stress of life activities Significant lead toward identifying cau es of cardiovascular (CV) disea e may be found in compari

sons between populations having apparently similar activity levels but exhibiting different degrees or types of physiologic responses. Heart rate, blood pressures, blood volume and composition, cardiac output and respiratory responses to customary activities represent only a few of the parameters potentially important in relating work to CV disease.

The work physiologist relies on work and recovery pulse rates as important indicators of over-all CV strain produced by activity. A lower pulse rate is held to be consistent with less CV *strain and greater cardiovascular fitness*. Cardiologists rightly point out types of CV abnormality in which such interpretations may be erroneous. Actually we cannot recommend sole reliance on pulse rate or any other single parameter as a measure of CV strain.

Burgher has again pointed out (Burgher, G. C. E., and Marten, G. A., Proc. XII Internat. Cong. Occup. Health 3:113-118, 1957) the desirability of using pulse pressure during activity in conjunction with pulse rate, and has demonstrated how such values may be utilized to derive an index of heart work.

(2) Standard Activity

In comparing populations having different activity levels it will often be useful to know the responses to a standardized level and kind of activity. Presumably such activity would be selected to lie within the *competence* of most members of the population under study. Walking on the level or up a moderate grade is probably the best activity for these purposes. The most meaningful physiologic values will be obtained after subjects have been exercising for some time and have acquired such a "steady state." Recovery pulses, blood pressures, etc., will also have some meaning (cf. Johnson, R. E., Brouha, L., and Consolazio, F., Rev. Canad. Biol. 1:491-503 (June) 1942). The Masters stepping exercise might be modified for this purpose but probably will not be suitable at standard pace because it represents heavy work (classification of Christensen, loc. cit., based on data of Ford, A. B., and Hellerstein, H. K., J.A.M.A. 164:1868-1874 (Aug. 24) 1957) in which a steady state will ordinarily not be achieved by most subjects.

(3) Maximum Activity

Knowledge of the maximum capacities and limitations of the CV system would be useful *in comparing populations* and especially *in* studies of the time course of change in capacity among groups with different activity patterns. Such information could also provide an objective check against acceptance of subjects' exaggerated claims of physical prowess.

The problem of estimating maximum capacity for work for middle-aged and older subjects is difficult because we will not accept risk of injury and to require maximum effort may or may not involve such risk. The need is for a means of determining capacity without requiring maximum effort. While there is no established reliable means for accomplishing this, leads have been provided. Astrand (Thesis from Gymnastika Centralinstitute, Stockholm, 1952) in his study of working capacity of normal subjects in relation to age showed that heart rate at submaximal work levels can be used to predict maximal levels of work output with fair accuracy. His subsequent research has been designed to evaluate this concept for less fit and older populations (results not yet available).

German (Muller, F. A., Freiburger Symposium, Heidelberg, Springer Verlag, 1958) and Dutch workers have been predicting maximum level of sustained work by measuring pulse response to increments of work on the

bicycle ergometer * The exercise may be terminated at a level predetermined as safe (e g 125 or 150 beats per minute), or on the basis of ECG changes The curve of heart rate against work is then extrapolated to 180 beats per minute (or a lower value for an older subject inferred from Robinson S Arbeitphysiologie 10 251 1938) The validity of such predictions depends on the degree of extrapolation that is required We would endorse support of studies further to develop and define the accuracy and sensitivity of predictions of work capacity based on heart rate and/or respiratory ventilation

The extra circulatory burden of exposure to warm environmental conditions during a performance test may be considerable (vide supra) For example our computations using Robinson s data (loc cit 1945) indicate extra demands of 1 5 liters per minute or more for cutaneous circulation when men are resting in heat and up to 3 0 liters or more when they are working It is clear that thermal stress must be minimized or controlled in application of tests such as those described above Research may be warranted to determine the usefulness of responses to thermal stress (in lieu of exercise) as a measure of cardiovascular status and capacity

C General Observations

(1) Prospective vs Retrospective Studies

The working group spent some time in weighing the opportunities for gathering information on physical activity in relation to development of CV disease (1) when the population is chosen for a longitudinal study in advance of major CV incident and (2) when the population is chosen afterward The cost of the two types of approach is not our direct concern but since the prospective type of study costs much more the results of our deliberation on this subject may be of interest.

It seems to us that the possibility of collecting accurate data regarding level and type of physical activity is much greater while the subject is well The present average and peak levels of activity and the physiological responses to work are directly observable After sickness is recognized these advantages of direct observation are lost and the prospect of obtaining an unbiased accounting of prior total physical activity from the subject or observers is lessened because of the vagaries of memory To the extent that there is a long term employment record on members of the study population this disadvantage will of course be less important

(2) Two Approaches in Study of Physical Activity

The information needed and the methods in attempting to find relationship between physical activity and CV disease will vary with the type of approach that is intended We recognize two major approaches study of two or more population groups assumed to differ in physical activity and study of a single population supposedly with diverse activity levels and attempting to classify its individuals as to physical activity

(3) Study of Populations Selected by Occupation

When the study is of the first type the energy demands and type of work should be ascertained by direct observation by a work physiologist using technics for sampling oxygen consumption of special activities and time study as required with view to ascertaining average total energy requirement and peak energy requirement and distribution of deviations from average Such

* See also Correlation of Static and Physical Endurance USAF IA A Test of Physical Performance Based on the Cardiovascular and Respiratory Responses to Gradually Increased Work Bruno Balke USAF School of Aviation Medicine Randolph Field Tex Project No 21-32 004 Rep No 1 1952

data are necessary to show how different the two populations really are Sufficient data on employment history must be examined to assure that employment has been (or in prospective studies will continue to be) stable

A representative sample of each population should be chosen (minimum requirement) for administration of an interview designed to establish average and deviations from average total daily activity as well as maximum activity levels over the adult years The same sample should be subjected to body measurement so that homogeneity or differences in build may be established for groups that are to be compared (vide infra)

It would be desirable to have total activity and body build data on the total population as a basis for sorting out subjects who are atypical It is also desirable to have information on current cardiovascular status of the sample or the full population whether available exercise tests can define cardiovascular status sufficiently for purposes of epidemiologic studies is not known but we consider the likelihood promising

(4) Study of Nonhomogeneous Populations

When the study is of the second type of a population which is apparently nonhomogeneous as regards activity level and type it becomes necessary to classify each individual on the basis of physical activity This should be accomplished by interview of all members of the group In addition it would be desirable to test the validity of interview data by administration of the same interview to associates at work and to friends as well as by examination of employment records

Categories of work that may be differentiated are light moderate and heavy as regards average physical activity Peak level may be classified as high moderate or low For those having moderate to high level peak activities it may be useful to differentiate primary requirements of speed (intermittent muscular contraction) endurance (for extended periods) and strength (lifting pushing carrying and so forth)

Minimum acceptable measurements of body form will be needed on all members of the population

Comments made above regarding desirability of measures of CV function and capacity through exercise tests are equally applicable in this type of epidemiologic study

(5) Retrospective Studies

Some parts of these observations have been applicable only to prospective studies It is recognized that direct measurements will have reduced usefulness in studies of factors related to onset of CV disease using populations in which heart disease is already present When the interest is in progress of CV disease after its first manifestation some of the direct measures will still be applicable

3 Body Form*

A *Information to Be Sought*

Body form may be related to the occurrence of cardiovascular disease (a) directly through some unsuspected or uncontrollable mechanism (genetic linkage) or (b) indirectly via some other factor(s) now thought to be associated with cardiovascular disease such as occupation biochemical status physical activity or diet

Even if the primary association of body form with cardiovascular disease is stronger than its association with other atherogenic or hypertensogenic factors the causality is obviously not direct that is body form does not in

* The Working Group expresses its appreciation to H T E Hertzberg W W Howells and W M Krogman for suggestions which appear in this section

itself cause di ea e As in all epi demiologic tudies the underlying mechani m will till have to be sought in the laboratory

(1) R lat on to Card ovascular D sease

Other committees be ide this one—pecifically those on pathology and genetics—have cited the evidence for an a ociation between body form and coronary heart di ea e Such evidence comes from two ets of investigators u ing the omatotype technic for de cribing body build Gertler M M and White P D (Coronary Heart Disea e in Young Adult Harvard University Press 1951) working with clinical material characterized young coronary patients as predominantly meso morphic (bony muscular) and econd arily endomorphic (round fat) Spain D M Brade s V A and Huss G (Ann Int Med 38 254 277 (Feb) 1953) on autopsy material called such *patients predominantly mesomorphic In* a later tudy Spain D M Bradess V A and Greenblatt I J (Am J M Sc 229 294 301 (Mar) 1955) reported that among endomorphs and mesomorphs but not ectomorphs (linear a thenic) coronary clerosis paralleled serum beta lipoprotein levels The consi tent results of these two ets of investigators require confirmation with additional measures of body form and with better controls For example 27 of Gertler and White s 100 coronary patients but very few of their unmatched controls were Jewish

Many reports too numerous to cite relate hypertension to stocky rather than lean builds Hippocrates was merely the first to note the apoplectic habitus Malignant hypertension has however been said (Pereira G A and Damon A Arch Int Med 100 263 265 (Aug) 1957) to occur in women significantly leaner by the height/cube root of weight index than women of the same age from the same clinic with either benign hypertension or no known di ea e

The tocky mu cular phy ique reportedly prone to both types of cardio va cular disea e coronary heart di ea e and hypertension thus contra t harply with the lean phy ique found more us ceptible to tuberculo is in recent large cale pro pective tudies both in England and the United States (Berry W T C and Nash F A Tuberclc 36 164 171 (June) 1955 Palmer A E Jablon S and Edward P Q Am Rev Tuberc Pulm Di 76 517 539 (Oct) 1957) So once more Hippocrates may have been right in contra ting the phthi ic and apoplectic habitu

(2) Relation to B o hem cal Fact s

Since Mia nikow (1851) many investigators have reported that cholesterol is higher in those of tocky than lean body build This has recently been uggested as an a sociation with body fat rather than muscle (Key A Ander on J T Fidanza F Keys M H and Swahn P Clin Chem 1 34 52 (Feb) 1955) (Miller D C Trul on M F McCann M B White P D and Stare F J Diet Blood Lipids and Health of Italian Men in Bo ton Ann Int Med 49 1178 1200 (Nov) 1958) and (Tanner J M J Physiol 115 371 390 (Dec) 1951) To distingui h fat from muscle Keys and Miller u ed kinfold Tanner u ed both skinfolds and somatotype

The consistent relation hip noted be*tween body fat and erum cholesterol* is low with a coefficient of correlation at best 0 40 though tatistically significant However muscularity of build said to characterize persons particularly su ceptible to coronary heart disea e has with equal consistency hown no relation whatever to erum chole terol level This is puzzling in view of the well documented elevation of erum

cholesterol among patients with coronary heart disease Perhaps Dr Spain hypothesis of a lower threshold for atherosclerosis among muscular persons *afford an explanation More research* is obviously needed on this point

(3) Relation to Occupation and Physical Activity

Since Morris work (Morris J N Heady J A Raffle P A B Roberts C G and Park J W Lancet 2 1053 1057 (Nov 21) 1953) on British bus drivers and conductors and on postmen and telegrapher occupational differences in coronary heart disease have been attributed to energy expenditure However there is a real possibility that self or job selection result in a concentration of certain types physical or constitutional in certain occupations Morris himself recognized this possibility finding that bus drivers had larger waists than conductors on entering service with the bus company (Morris J N Heady J A and Raffle P A B Lancet 2 569 570 (Sept 15) 1956) Previous independent work *on American bus and truck* drivers showed that they were more mesomorphic and stockier than the general population (Damon A and McFarland R A Am J Phys Anthropol 13 711 742 (Dec) 1955) The same authors indicate that consistent physical differences have been reported among occupations and adduce evidence that these are not caused by the occupation (Damon A and McFarland R A J A M A 153 622 625 (Oct 17) 1953)

In a recent letter Dr Morris informs us that further analysis of morbidity and mortality data among bus drivers shows plenty of heart disease among both fat and thin However fat drivers have more heart disease than fat conductors and thin drivers have more than thin conductors Here again is an area which needs further study

B *Methods for Obtaining Information*

Descriptions of body form for studying correlations with cardiovascular disease are obtained from height weight and other anthropometric dimensions skinfold thickness somatotypes strength tests and physicochemical analyses of body composition The last four techniques attempt to supplement the useful height weight relationship by apportioning total weight or bulk among various tissue and compartment particularly distinguishing muscular bony from fatty components

(1) Height and Weight

Height and weight are minimum essentials and should be taken as nearly nude as possible The practice of permitting light clothing and footgear has vitiated several large and expensive studies If some clothing must be worn —and sock shorts and brassiere may have to be permitted—several representative clothing samples should be weighed to give an accurate subtraction constant

These basic dimensions should be taken with the care expended on the ECG and cholesterol determination Sloppy technic by untrained or unsupervised technicians is all too common

Height should not be taken with the bar attached to some medical balance scales but preferably against a flat wall without a molding at the base with the subject instructed to stretch to his maximum height and to take a deep breath Printed engineering strips ruled in inches and tenths or in centimeter are satisfactory for pasting on the wall A cigar box or other right angled block can be slid down the wall until firm contact is made with the head oriented in the horizontal eye-ear plane (top of external auditory meatus and inferior margin of bony orbit) If a scale bar must be used it should be calibrated first and again the subject urged to stretch and tapped in the lum

bar region to facilitate thi An anthropometer is acceptable but only in the hand of a trained person

Weight hould be taken preferably on a medical type of balance scale to the nearest pound height to the nearest millimeter on an anthropometer tenth of an inch on printed strips or quarter inch if the scale bar is so calibrated

Almost as important as current weight is weight hi tory as detailed as possible Inquiry hould be made—and checked by objective records if possible—as to maximum weight age when attained its duration and cau e (in activity illness pregnancy) rea on for weight loss if any and duration of current weight It would be desirable to reconstruct weight during each decade of adult life Weight can often be recalled in connection with athletic participation military service marriage or pregnancy Each figure should be pecified as with or without clothing Of course such objective data involve considerable error A rough check on reliability is afforded by asking the subject his current weight before weighing then comparing the two figures

(2) Index of Body B ld

U e of the data once obtained is not strictly within this subcommittee s purview but the utility of the ponderal index height/cube root of weight, as a simple generalized description of body build is worth noting Though not distingui hing between the fat and bony mu cular components of body bulk its distribution is known in several izable population amples and promising correlations have been reported with occupational choice physiology and di ease Attention should al o be drawn to the widespread but unfortunate custom of expressing perfectly good nude heights and weights as percentages under or overweight based on clothed standards of dubious applicability to the populations being studied

(3) Skinfolds

These are u eful correlating about 0 70 with body fat and with endomorphy An excellent in trument the Lange skinfold caliper is available from the Wenner Gren Aeronautical Laboratory of the University of Kentucky

The two preferred sites for mea urement are triceps and subscapular Technic is extremely important ince slight variations in method and location of site can make major differences in readings The technician mu t be trained and at least initially checked by a skilled professional The ame technician should take all the mea urements in a given urvey if possible

(4) Circ mferences

Upper arm circumference at the level of the skinfold chest circumference (in males) waist circumference eat (hip) circumference and maximum calf circumference are desirable Of these only the first is recommended a a minimum essential (but ee below) by the National Research Council Committee on Nutritional Anthropometry (Brozek J Body Measurements and Human Nutrition (Ed) Detroit Mich Wayne Univer ity Pres 1956) These are all horizontal with minimal pre sure and made with a millimeter teel (not cloth) tape Keuffel and Esser Wyteface or Lufkin All circumferences are measured three times as are skinfolds recording the best single figure Chest circumference is mea ured during quiet breathing

(5) B acromial and B l ac D meters

Though recommended by the NRC Committee on Nutritional Anthropometry and though theoretically useful in indicating laterality of build these two skeletal dimensions alone have so far proved much less relatable to behavior

physiology or disease than ratings of morphological masculinity and femininity based on additional criteria This is true whether these dimensions are analyzed separately added related to stature separately or combined or when related to one another as an index of morphological masculinity (Seltzer C C Psychosom Med 8 75 97 (Mar Apr) 1946) (Damon A and McFarland R A J A M A 153 622 625 (Oct 17) 1953) (Miller D C Trulson M F McCann M B White P D and Stare F J Ann Int Med 49 1178 1200 (Nov) 1958) Further more they require anthropometric skill and are worse than useless unless so taken Since these measurements are currently being taken in several surveys it may be premature to discard them until all the evidence is in For the present it seems best to retain them along with upper arm circumference as on the borderline between minimum acceptable and desirable until their value is proved or disproved

Unless biacromial and bi iliac diameters can be measured accurately and reliably which requires training they should not be taken at all

(6) Sitting Height

This is a desirable measurement, since it varies with sex race and body build and since—by subtraction from stature—it provides a measure of leg length a useful tailoring dimension along with chest waist and seat circumferences In retrospective studies such as those current at the Johns Hopkins and Albany Medical Schools (Paffenbarger and Krueger this conference) clothing size may provide data not otherwise available on body dimensions With height and weight such data permit an approximation to body build

(7) Hand Grip Strength

This correlates about 0 57 with forearm girth largely muscle (Lindegoard B Acta psychiat et neurol Suppl 86 pp 1 163 1953) Strength may also be related to energy expenditure

(8) Photographs

These provide a permanent record of what the subject looks like From photograph reliable measurements of body diameters can be made especially if the anatomical landmarks have been marked on the subject One may also obtain somatotypes hair patterns masculinity rating and planimetric determination of body areas and even volumes if front side and back poses are available Since the strongest evidence for an association between body form and coronary artery disease comes from somatotyping it seems logical to recommend this photographic technic (Sheldon W H Varieties of Human Physique 1940 Atlas of Men New York Harper 1954) Other photographic technics may be as good or better but none has received so extensive a trial (Tanner J M and Weiner J S Am J Phys Anthropol 7 145 186 (June) 1949 and Gavan J A Washburn S L and Lewis P H Am J Phys Anthropol 10 331 353 (Sept) 1952) The important point is to photograph at a standard distance with a known magnification factor and with the subject carefully posed in the three standard views A 90° turntable is desirable

(9) Research Technics

Research technics well worth investigating but not as yet suitable for epidemiological studies include method for analyzing body composition in the living such as densitometry gas and dye dilution body water partition and radiography (Keys A., and Brozek J Physiol Rev 33 245 325 (July) 1953)

The ultimate logical step is to study the mechanism underlying those associations between body form and cardiovascular disease which with fur

ther work remain firmly established One such research area being studied by Dr Spain is the correlation between body build and endocrine status Another is the correlation between body build and organ or tissue morphology

Summary

Subject to later revision if warranted by experience the following measurements of body form are proposed for epidemiologic studies of cardiovascular disease

Minimum Acceptable Measurements

Height
Weight—plus weight history in as much detail as possible
Skinfolds—subscapular and triceps
Biacromial and bi iliac diameters
Circumferences—upper arm chest (in men)

Desirable Measurements

Seat waist, calf circumferences
Sitting height
Hand grip strength —Collins-type dynamometer carefully calibrated Narragansett Gymnasium Equipment Co Centralia Mo
Photographs—front side and back poses

Conclusions

(1) We reiterate that when physical activity is of concern in epidemiological studies knowledge will be required of average daily energy expenditure the pattern of activity as regard peak levels and timing and the physical environment in which activity is performed—all over a period of years

(2) In many studies it will be desirable to know the physiological response of our populations to physical activity in terms of cardiovascular strain involved *in performance of accustomed* activities and of a standard work task The best available single index of effective cardiovascular capacity is maximum rate of oxygen uptake (or the energy equivalent of such uptake)

(3) Our definition of energy expenditure levels in terms of light moderate and heavy with caloric expenditure levels designated for each is useful in epidemiologic studies The description of the standard man to whom such caloric values apply and a method of finding the equivalent caloric values applicable for nonstandard men are spelled out

(4) When feasible record of dietary intake should be utilized to check estimates of total energy expenditure obtained from analysis of physical activities

(5) The cardiovascular stress of physical activity may be more directly represented by an index which utilizes heart rate and blood pressure than by an index of caloric expenditure In other word energy expenditure does not always reflect heart work However one measure is not a substitute for the other When an hypothesis call for investigation of relationship between heart work per se and degenerative CV changes a heart work index will provide the information that is most directly relevant However when biochemical or physical concomitants or by products of muscular action are being examined in relation to cardiovascular change energy utilization is the information that will be most directly useful

(6) We reiterate that minimum acceptable measurements necessary for description of body form are height weight (with history) skinfold thickness and key circumferences and diameter Such information on morphology should probably be a matter of record in all studies of concern to this conference The information will of course be essential in studies where the focus is on diet or activity Other measurements of the given list are desirable when it is feasible to obtain them

Recommendations for Research on Methodology

(1) Method should be sought for determination of blood pressure during work This would enable derivation of useful indexes of heart work based on appropriate combinations of heart rate and blood pressure values

(2) Methods should be developed for monitoring and recording blood pressure and heart rate over extended period This would give information of value in judging cardiovascular cost of the complex tasks which make up a day's activity

(3) The reliability of information obtained by various technics of questioning and interviewing on physical activity should be verified by direct observation

(4) Means should be developed and validated for predicting maximum oxygen utilization without requiring maximum work First efforts should be directed toward finding the reliability of prediction of maximum work capacity based on physiological responses to systematic increases in work load from light to moderate

(5) Statistical procedures for work sampling should be developed as a means for determining energy requirements of various occupations

APPENDIX 1

Outline of Methods for Measurement of Physical Activity (with Key References)

1 Energy Expenditure (respiratory volume oxygen utilization)—Estimate from oxygen consumption (with or without CO_2 production) Method involves metering of expired air collection of total volume or aliquot sample measurement of oxygen content (CO_2 content) computation of energy consumption as oxygen utilization x 4 9 (approximate) =calories energy Weir has provided a refinement of computation which takes protein metabolism into account[1]

Precautions Arrange apparatus to encumber subject as little as possible In describing energy requirement of a task obtain repeat measurements if possible on different subjects Attempt at showmanship on part of subject can markedly alter level of activity and timing of task to point where representative values are not obtained For high level activities measure O_2 uptake by the so called integral method at rest before and during work and recovery so that anaerobic as well as aerobic cost of effort may be assessed Cost of work depends on the muscle groups involved energy cost of locomotion depend more on body mass than surface area so expression in KCal per unit weight is preferable

(a) Classical method involves collection of expired air in Douglas Bag or spirometer later metering and collection of sample for analysis, analysis of sample for O_2 and CO_2 with Haldane apparatus[3,4]

(b) The Max Planck Institute at Dortmund has developed a device[5,6] which meters expired air withdraws 0.3 to 0 6 per cent of total for analysis Device requires calibration at various rates of air flow

(c) Wolff has developed an integrating Motor Pneumotachograph (IMP)[7,8] for measuring volume and collecting sample It is the lightest device available and has been used continuously for periods of many hours Sampling period should be more than 10 minutes

(d) Pauling[9,10] has developed simple means for determination of O_2 in expired air depending on paramagnetic properties of gases Dial reads directly in per cent or partial pressure of oxygen Faster and requires less skill than the Haldane method accuracy sufficient but not as good as Haldane

(e) If required CO_2 in expired air can be analyzed by infrared gas analyzer[11]

(f) Time weight of individual tasks will usually be necessary to derive value for total energy cost of job Example of procedures is provided by Morris[1]

2 Pul e Rate

(a) By manual palpation Radial pulse may not be accessible without disturbing work in which case carotid may be convenient site of palpation Po texertional pulses have meaning for certain tests of fitness but should not be relied upon as index of grade of work *previously performed*

(b) By EKG or cardiotachometer Heavy muscular efforts and sweating make accurate measurement by these means difficult. Use of chest lead helps reduce static"

(c) By pickup from photensensitive element which follows changes in opacity of the ear

(d) A general reference on these systems is provided by Dill[13]

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APPENDIX 2

Check List of Items to Be Covered in Que tionnaires on Phys cal Activ ty

Off the Job Activities

- Routine current activities—hours and maxi mum effort
  - Regular exercise—sports walkin, ama teur professional competition
  - Home maintenance
  - *Hobbies*
  - Transportation (walking to work etc)
- Attitude toward exercise
- Amount of sleep
- Hi tory of phy ical activity
  - School and college changes since—relate to weight history

On the Job Activities

- Present job—duration
  - Hours vacations lay offs
  - Title
  - Job description—what do you actually do
  - Maximum efforts—rest periods—periods of intense activity
  - Proportions of sedentary standing walk ing climbing etc
  - Heavy lifting—Heat stress
- Previous jobs—general type and details as above—p riods of unemployment
- More than one job
- Attitude toward job

SUBCOMMITTEE ON BIOCHEMICAL MEASUREMENTS

Forrest Kendall Ph D Chairman

THE Subcommittee on Biochemical Measurements considers that its task in this conference is

I To discuss the place of biochemical measurements in epidemiological studies of cardiovascular diseases

II To set up criteria for judging the suitability of any specific biochemical measurement for such a study

III To outline the procedures required to achieve comparability of measurements made in various participating laboratories throughout the duration of the study and

IV To recommend a plan for implementing a system of controls necessary to achieve this comparability between laboratories

I The primary purpose of any epidemiological study is to evaluate the influence of diverse genetic and environmental factors upon the occurrence and severity of a disease We all recognize that the achievement of this purpose in the field of cardiovascular disease is of the utmost importance and of the utmost difficulty This is particularly true for atherosclerosis and hypertension No one has succeeded in demonstrating specific etiological agents for these disease However marked differences in the occurrence and severity of these diseases in different population groups support the hope that epidemiological studies may succeed in defining the factors which cause them Two obvious difficulties of applying epidemiological technics to the study of these diseases are the chronic character of *the diseases and their presence in* occult form in a considerable portion of the population Factors leading to the development of these diseases may be operative over a period of many years before clinical manifestations are recognized

The problem would be simplified if it could be shown that a cardiovascular disease produces some characteristic biochemical change which appears before clinical symptoms become manifest and which disappears when the cause of the disease is removed Much research in the field of atherosclerosis has been undertaken in the hope of showing that the concentration of some substance in the blood is as useful diagnostically in this disease as the level of glucose is in diabetes mellitus The presence of abnormal deposits of cholesterol and other lipids in the lesions of atherosclerotic arteries has focused attention upon the relationship between serum lipid level and the presence of diagnosed atherosclerosis Studies have been made of the relationship between coronary atherosclerosis and the serum level of cholesterol of phospholipid of cholesterol phospholipid ratios of alpha and beta lipoprotein of triglycerides and of chylomicron Some degree of correlation has been found to exist between the level of each of these factors and the disease Although the differences between the mean level in diseased and control group are statistically significant the values for the two groups are distributed over very similar ranges and have little diagnostic or prognostic significance for any given individual

It is interesting that this statement could have been made immediately after the publication of the first study of the *distribution of serum cholesterol level* in the serum of patient with coronary heart disease and a control group It was shown at that time that the serum

cholesterol values were distributed over similar ranges in both groups although the distribution curves tended to be skewed in favor of high levels in the coronary patients. Subsequent surveys have only served to confirm the original observation: they have added more points on the curve but the curves have not changed. It is *unlikely that additional* work to increase the accuracy of the methods for either sampling the population* or of determining the serum cholesterol *levels will add substantially to the usefulness of serum cholesterol* levels as a means for diagnosing the presence of atherosclerosis. Surveys that seek to relate biological levels with the disease are not strictly epidemiological studies in spite of the fact that large groups of the population are being surveyed. They still remain in the category of clinical investigations because they do not relate the disease to *specific environmental or genetic factors* which characterize the population under investigation. The biological level of a *substance in an individual is not neces*sarily a characteristic of that individual but may reflect environmental factors.

In many studies a biochemical determination has been substituted either for an adequate study of these factors *or for an adequate appraisal of the* clinical manifestations of the disease. This procedure is valid only if it is known with *certainty* that the disease is directly *related to the biological level* of the substance measured.

At the present stage of our knowledge the assumption that the biological *level of any substance is an etiological* factor in the development of atherosclerosis may obscure rather than illuminate the significance of an epidemiological study. Thus populations consuming high fat diets tend to show an increase in serum lipid level as well as an increased *incidence of coronary* atherosclerosis. These two phenomena may be related to each other only by occurring simultaneously in many individuals. The high serum lipid levels may be a direct result of the presence of large amounts of fat in the diet, while the development of the *lesions may be* due to some other environmental factor which varies systematically with changes *in the fat content of the diet.*

An epidemiological study should be so designed that the biochemical data are not introduced into the scheme of the study as an intermediate factor B associating A, the *environmental* and genetic factors, with C, the disease:

A → B → C

Evaluation of a possible relationship between B *and* C *may* be one of the purposes of the study, but the survey should be set up in such a way that the effect of A upon B and C is assessed independently.



The placing of cholesterol between the environmental factors and the disease has resulted in a widespread tendency in the medical profession to treat the hypercholesterolemia in their patients as though they were treating atherosclerosis. It has been found that various types of medication will result in a reduction of serum cholesterol levels. Nicotinic acid, for example, will reduce the serum cholesterol level and many other things will do it equally well. Epsom salts is as effective perhaps as nicotinic acid. Persistent diarrhea *reduces serum cholesterol* levels very well indeed, but does it cure atherosclerosis?

An outstanding scientist recently made the statement that he thought our preoccupation with serum cholesterol

* Choice of population samples for study of atherosclerosis poses many problems. General populations are depleted by deaths due to atherosclerosis and other diseases but include many persons who have atherosclerosis without clinical manifestation. Better diagnostic tests would simplify sample selection.

levels had resulted in the most flagrant example of tubular vision he had encountered in the field of medicine and that he felt sure that this preoccupation had prevented us from seeing and recognizing relationship that certainly exist between environment and the disease

It is possible that the most valuable function of biochemical measurements in studies of this type is to permit the selection of certain segments of the population to be subjected to a far more complete analysis than can be applied to the whole population. Thus studies of the background of the individuals who develop symptoms of coronary atherosclerosis in the presence of low levels of cholesterol and beta lipoproteins in the serum or of individuals who do not develop symptoms of the disease in spite of persistent high levels may succeed in helping to define the epidemiological factors responsible for the disease

II To be useful in an epidemiological study a biochemical measurement must fulfill certain minimum requirements

(a) The level of the substance measured should not be subject to wide fluctuation dependent upon factors which cannot be controlled under the conditions of the study. To cite an example. The level of the unesterified fatty acid in the blood which may turn out to be a very important factor in this disease process is so dependent upon the dietary intake physical activity and emotional status of the subject that study of this important biochemical factor could not be expected to yield significant information in an epidemiological study without extraordinary care in setting up basal conditions

(b) The concentration of the substance in the biological sample should not be subject to significant change between the time the sample is collected and the time when it is analyzed. This would perhaps rule out many determinations which might yield valuable information if proper preservative techniques are not available. This is particularly true of the concentration of various enzyme substances in the serum

(c) Analytical methods must be available that will yield reproducible results under all the working conditions likely to be encountered geographically throughout the study. Some methods which are satisfactory in temperate climates fail completely under abnormal conditions of temperature and humidity

(d) The method selected should give valid results over the entire range of samples that might be encountered

Thus some methods for the determination of serum cholesterol levels yield invalid results when applied to lipemic or hemolyzed sera or to samples where the concentration lies outside a small restricted range

(e) The method selected should be one that can be performed with technical adequacy by the laboratory personnel available. Many methods which yield reproducible results in the hand of a highly skilled investigator are too difficult for the average technician

III The problem of insuring comparability of biochemical measurements made at different times and by different laboratories is not solved by the selection of a valid method. Reports comparing the values obtained by different laboratories for the concentration of various serum constituents in replicate samples of the same serum reveal that intolerable differences occur unless a systematic effort is made to insure comparability. This difficulty is not one that is unique to epidemiological studies. It exists wherever biochemical measurements are made. It may be due to internal factors existing in individual laboratories that result in failure to obtain consistent results from analyses performed on the same sample on different days. It may be due to external factors leading to differences in the analyses performed by the various participating laboratories. Precise informa

tion concerning the cause of these difficulties is urgently needed

In 1958 the National Heart Institute and the Communicable Disease Center initiated a pilot standardization program with the cooperation of five laboratories interested in *epidemiological* studies. The purposes of this project were (1) to investigate the usefulness of statistical methods for the detection *and control of factors which contribute* significantly to variations in total cholesterol values within and among laboratories and (2) to determine the practicability of using lyophilized human *serum as a standard reference material* for total cholesterol determinations. The study showed that statistical analysis of the results obtained by introducing a small number of previously analyzed samples in each day's workload permits rapid recognition of failure to achieve internal reproducibility

The participating laboratories analyzed duplicate samples of lyophilized serum from each of four serum pools containing graded concentrations of cholesterol. The analyses were repeated every three weeks for a 15 week period. In this time three of the laboratories did not differ significantly among themselves. *The fourth consistently reported* higher values than the others. No secular changes were observed. These results suggest that lyophilized human serum can serve as a reasonable reference standard

IV Up until the present time every epidemiological study has had to find an independent solution of the problem of insuring comparability of biochemical measurement. The committee is of the opinion that the time has come when it would be economical for the organizations that sponsor this conference to take some action toward *setting up* a system to help achieve this *comparability*. *We believe that this* would be done best by the establishment of a central laboratory which would have the following five purposes

1 To act as a central intelligence agency in order to maintain communication between laboratories and interested organizations carrying out specific measurements

2 *To prepare characterize preserve* and distribute standards which can be used in the calibration of particular methods. This is a particularly important function that should be taken over by a central organization. We all remember how a few years ago the service performed by the Bureau of Standards in providing accurate *primary standards in many different fields* of analysis played an important role in the development of chemistry in America. This function is no longer necessary in most fields but it is still needed in the field of biological chemistry. It may not be possible to buy a sample of cholesterol that is pure enough to depend upon as a working standard for the determination of cholesterol. Each individual laboratory seems to be expected to know just how to prepare this necessary primary standard from commercially available cholesterol. Provision of a cholesterol standard would help obtain comparable results from *different laboratories. Trustworthy* standards are even more important in other fields e g reliable standards for measuring prothrombin time. If this central organization did nothing but provide standard materials to enable the participating laboratories to check their results, it would serve an important function

3 *To furnish consultative advice on* biochemical methods to interested and qualified laboratories

4 To compile and publish the experience and performance records of calibration studies

5 To act as an international clearing *house for the exchange of biochemical* information pertaining to the solution of methodological problems

COMMITTEE ON CULTURAL, SOCIETAL, FAMILIAL, PSYCHOLOGICAL, AND GENETIC INFLUENCES

Harry Kruse M D F.A.P.H.A. Chairman

Introduction

THIS committee of the Conference on Methodology was concerned with cultural societal familial psychological and genetic influences in relation to cardiovascular disease This postulated association is commonly based on the following assumption cultural societal and familial situations may create stress in the individual leading to or adversely affecting cardiovascular disease Why some persons react pathogenically to stress and why only certain of them have their cardiovascular system involved are questions usually explained by attributing this electivity in part at least to genetic influences

Implicit in this hypothesis is the belief that stress may either contribute to the development of coronary disease or at least, adversely affect the clinical course of the established disease Although at present there appears to be no consensus on the relevance and importance of stress in heart disease this possibility must continue to merit consideration until stress and its related circumstances have been demonstrated unqualifiedly to have little or no significance

Unfortunately the concept of causation—and of stress for that matter—may be so vague or oversimplified as to be misleading Today causality of disease is seldom visualized in the old simple relationship that A produces B Rather a holistic concept of causation envisioning a constellation of diverse factors is held Essentially these factors fall into three main groups (1) those in the environment using the term broadly to cover both the physical and social environment (2) those in the host or individual and (3) those associated with the adverse agent or process whether it be an excess a deficiency or an interference The multiple individual factors subsumed under these headings vary in their onset rate intensity and duration Thus they have their own particular characteristics and functions in the constellation and make distinctive contributions to causation Various names have been proposed to designate their characteristics and functions for example predisposing provoking precipitating perpetuating and conditioning factor and antecedent circumstances These names are of course not equivalent But one of the most important points to be borne in mind is that a factor that alone cannot produce a disease can determine whether the disease is produced With that in mind it should be obvious that, in the present state of knowledge the flat statement that stress has a minimal significance in heart disease is seriously misleading Until it has been irrefutably demonstrated whether stress is an active component in the causal constellation and until the nature and extent of its participation have been clarified it is impossible to evaluate its significance with finality

In its nature and its expanse the subject of this committee possesses characteristics unlike that of any other committee of the conference First, it com

prises varied topics each of which falls under a separate discipline. Each discipline has its distinctive group of specialist vocabulary and methodology. Second, despite this diversity all the topics in this subject are interrelated. For example, there are natural pairs: physical environment and the individual, the group and the individual, somatic and psychological environment and heredity. These pairs are interrelated not only horizontally but also vertically and diagonally. This complex interrelationship poses a problem. These topics are so closely associated that it is almost impossible to discuss each separately without some distortion arising from incompleteness. On the other hand, discussing these interrelationships necessarily involves repetition. Actually we should talk on all points simultaneously. But for present purposes that procedure would create grave disorder.

Third, although this is a Conference on Methodology, it was impossible in this section to exclude content. The design of any study depends on its objective; in turn, both the design and objective depend upon a hypothesis which must be constructed from content. Then too, inclusion of content was even more essential because of the multidisciplinary as well as intradisciplinary differences in subject matter, terms, and meanings. In consequence, this section had to be concerned with both the substantive and procedural phases of the subject.

The basic assumptions of the subject, its diversity, the interrelations and multidisciplines of its parts, and the operational sequence—all these considerations dictated the approach of this section. The subject was divided into four major topics, and the order of discussion followed the sequence outlined in the hypothesis describing their interrelation. These four broad topics were: stress, environment (especially social environment), type of person, and genetics. Thus the discussion started with the individual, then moved to group phenomena and finally returned to the individual. In each topic clarification and crystallization of content was sought before methodology was discussed.

From the standpoint of methodology it is useful to restate at this point the sequence of events in the thesis to be investigated. It is desirable to ascertain whether cultural, societal, and familial influences produce stress that may be linked with cardiovascular disease. A two-stage operation would probably prove best: (1) the relation of cultural, societal, and familial factors to stress, and (2) the relation of stress to heart disease. Of course it is possible to devise a one-stage operation which by-passes stress, namely, the relation of social environment to heart disease. Such a study would doubtless produce useful data; however, if the evidence were positive, the essential intermediate steps would be missing.

Stress and Adaptation

Because it occupies a central place in the course of events, the state of stress is the logical topic for first consideration. But there were also practical reasons. Enough is known about stress to warrant the supposition that it can serve as a valuable indicator of influences to be looked for in the environment. *Furthermore, if stress is demonstrated* to have any significant relation to heart disease, this fact becomes of utmost practical significance in the prevention and treatment of coronary disease.

In considering stress we are immediately confronted with its meaning and the number of terms associated with it and sometimes used synonymously: strain, load, pressure, tension. It is by no means certain that stress is the proper term for the phenomenon under discussion, but it would serve no useful purpose to cavil over terminology or to

draw di tinctions in meaning Never theles its developmental history i in formative

Twenty five centuries ago Hippocrate used the term stress in relation to di ea e and in general the current bio logical concept is remarkably similar to his view In the late eventeenth century the concept of stres came into promi nence in phy ics in defining the proper ties of gases and olid bodie On the biological side Cannon brought tre s from the philosophical into the cientific realm by analysis of the biological re action His reaction test however wa limited From observations on experi mentally induced stre s Selye greatly ex tended the boundaries of the concept with his demonstrations and v ews of the alarm reaction general adaptation syn drome and local adaptation syndrome Wolff and Hinkle further expanded the concept and filled in missing areas by their tudies on the ocial environment its effect and man s reaction to it

Currently the term tre s is applied biologically to indicate the state in an organism which results from reaction to noxious stimuli or di turbing situations However the group expressed ome re ervations over this interpretation In the group s opinion stre s itself is a concept combining both an abstraction and a generalization As an ab tract quality it characterizes a number of bodily states But the fact that tress i an abstraction is no rea on to avoid con sideration and u e of the term As it i usually described it is well recog nized Hence it wa agreed that as the term is u ed in biology and medi cine it ha understandable meaning man is facing difficulty To impart that meaning the term has u efulne It was decided however that it would not erve present purposes to attempt to differentiate and separate different type of tress such as acute or chronic emo tional or physical

It is useful to describe the nature of *stre s its meaning its production* the adaptive reaction which it elicits and its effects It cannot be overemphasized that the topic encompasses a eries of events with a potentiality for multiple processes at each tage

Man is exposed to two different kind of external environment physical and ocial Each in its own way exert its influence on him and each produces a different type of effect Here we are concerned with the di turbing not the beneficent influences

The physical environment including what we call nature has certain prop erties which affect man heat cold elec tric shock x rays pathogenic organi m and toxins By and large as a clas s they have a distinctive mode of rela tionship to the body of action and effects (1) They impinge directly upon the body (2) they di turb energy transformation by bringing about an increase or a decrease by withdrawal or interference and (3) they may de troy cellular form and function

Quite different is the ocial environ ment in its mode of affecting man Its influence ari es in ituations and per sonal interaction It is transmitted with out direct phy ical contact with the body Instead stimuli are received by man s en ory sy tem Out of the mul tiple impulses in an experience ome are selected and ummated The ensu ing ensation arou e a ociation mem ories and feelings In hort perception and evaluation occur As an ideational proces evaluation may not take place until some time after an experience U ually there is a succes ion of idea tional proce es with temporal projec tion both retro pective and pro pec tive memories other imagerie both imaginative and anticipatory and thought Meaning and value judg ments enter into the thought tate and feelings are aroused An attitude of di satisfaction may develop in an affec tive tate of unplea antnes

In evaluating a situation man takes into account the demands upon him and in turn his needs urging satisfaction all organized in a setting of circumstances and conditions For a variety of reasons the person may regard a situation as unfavorable To him it may appear to be threatening alarming overdemanding restrictive frustrating conflictive or unsatisfying It is well to reiterate that whether a situation in the social environment imposes a strain on a person depends upon his conception and evaluation of it Similar situations do not have the same meaning for all persons Indeed, a situation rated by a detached observer as undisturbing may not be so regarded by a person involved in it The opposite strangely enough is equally true

To unfavorable influences from both environments the body responds Either a disturbing physical factor or social situation may act as a signal whereby the body reacts in an effort to neutralize overcome and nullify the unfavorable influence to avert its further operation and to restore the body to its usual state This is the process of adjustment or adaptation in which the body responds as a whole physiologically biochemically and psychologically i e through bodily function mood thought and behavior Depending on the type of disturbance the reaction is mediated at various levels of the central nervous system For signals from a social situation the brain acts as an adaptive organ directing the mitigating opposing and restorative efforts of the body Since all parts of the human system are subject to participation in this adaptive reaction the tremendous potential of the brain for altering bodily function and behavior can scarcely be overestimated

The capacity for adaptation is not the same in all persons hence success in adaptation is variable How well man reacts to a situation in the social environment depends in part upon his conception of it When he perceives a life situation as oppressive obstructive or unsatisfying he may not be able to make a favorable adaptation

Somatic and psychological alterations occurring during adaptation may lead to diseases designated diseases of adaptation Their production has been variously explained It has been suggested that they occur as a result of inappropriate or overly sustained adaptation Another view is that disturbances of bodily function mood thought and behavior which occur during periods of adaptive effort make possible appearances of disease processes which might not otherwise manifest themselves

Ackerman has described in detail his views on the psychological processes comprising adaptation and the sometimes pathological consequences Three levels of phenomena are involved in the interaction between the individual and society the structure of the environment interpersonal relations and the inner psychic life of the individual Personality and society cannot be considered apart Human behavior is shaped both by the organization of the internal forces of personality and the external forces of society Social forces do not operate in a human vacuum nor does personality exist in a social vacuum Social forces are mediated through that phase of personality which achieves expression in group relations Hence in studying social phenomena the most serviceable definition of personality is that which emphasizes the orientation to social participation

The functions of personality are oriented in two directions (1) toward the internal processes of the organism and (2) toward the social environment There is continuous interplay between the two relations Together they constitute total personality In its position of interchange with the environment personality has a relative unity

Society is the medium in which the

identity of a person gradually emerges As the individual matures he achieves an identity which is at once both individual and social He has an individual self and a social self The individual component of personal identity is represented in the more durable less modifiable aspects of character structure It is the core of the personality the more personal private relatively fixed aspect of self It reflects behavioral tendencies which have been conditioned by interaction of biological dispositions and family environment The social component of a person's identity is represented in the less durable more modifiable layers of character It is less personal less private less fixed It reflects behavioral tendencies which have been acquired later It is these relatively more external layers of character which permit the greater degree of penetration by social forces The social identity of a person reflects the continued interdependence of individual and society For present purposes we are primarily concerned with this social self representing those functions of personality which are externally oriented

Those operations of the social self in the context of a given life situation may be called social role Social role is the intermediate between intrapersonality life and group behavior being that integrative aspect of the total personality which is expressed in social action It implies the capacity of the personality to make fluid changes in form in accordance with the adaptational requirements of the individual's position in society In a given time and social situation certain components of the total self are mobilized into action and moved into a dominant position while other components are temporarily subordinated In essence this is the process of social adaptation By definition social role is the adaptational unit of personality in action

The psychic processes and combined components of behavior make up the configuration of social role Orientation in this action phase of personality presupposes a set of goals and values commensurate with the individual's position in a given group These values which provide directives for social action are derived partly from the individual personality and partly from group organization they are oriented toward both self and one's relations to other persons Their dual orientation involves (1) personal attitude toward one's individual striving and (2) quality of apperception of culturally dominant patterns of interpersonal relations

Out of the orienting coordinating functions of personality and the surrounding group forces there is crystallized a specific pattern of action which is reflected in the form of a particular social role Some of the components entering into the integration are apperception of patterns of interpersonal relations attempt to achieve gratification of inner need assertion or subordination of self compliance with or protest against social pressure effectuation of means for control of the environment selection of particular defenses against anxiety an effort to find solutions to personal conflict projection of inner conflicts into the social role These components determine value orientation and the corresponding configuration of the social role

The relative success or failure of adaptation in a given social role is the result of coincidence or conflict between character disposition and social environment There are numerous vicissitudes in the relation between social role and individual personality First, it is assumed that the normal person has the capacity to effect flexibly a variety of social roles in accordance with adaptational requirements But persons vary in the extent of their repertoire and they may be required to assume roles

beyond their range or out of character.

Second, the degree of psychic distance between the individual and social selves is significant. In emotional content the social role may be peripheral or central to the individual self; hence it may have central or peripheral significance in relation to the individual's emotional life. Such relations will determine the degree to which an individual's identification with a group is genuine or false, spontaneous and healthy, or forced and anxiety ridden.

Third, the amount of anxiety generated is influenced by the degree of harmony or conflict between individual identity and social identity. The person's inner concept of self either may coincide with the aspect of self projected into a particular social role or may clash with it. In the event of conflict, anxiety is generated with profound effects on social role. It may induce increasing instability and a tendency to rapid change of roles. Or it may induce increasing rigidity. In either event adaptive efficiency is impaired. Thus the personality performance in a given social role is affected by the relative harmony or conflict between the social expression of self and the inner evaluation of self.

In this process of social adaptation the individual may react to social pressure in four ways: compliance, protest, withdrawal, new integration. It is the latter reaction which is of particular interest. New integration occurs when social pressures are overwhelming and exceed the individual's resources for pliable adaptation. Sometimes the dilemma of more than one role brings on the crisis. This situation occurs when a person faces two antithetical roles and is incapable of assuming either, or when he must perform two roles but their conflicting nature prevents performance of them. The consequence of the unresolved conflict between the emotional content of antithetical roles is an adaptive breakdown of the characteristic and usual social role. Then the person responds with integration of a new form with distinctive properties of its own. This process seems to occur in the development of the so-called psychosomatic disorder.

Through physiological arrangement in the course of adaptive reaction any bodily function subject to the regulation of the central nervous system might be influenced to a significant degree. That regulatory influence might be mediated directly by any of the nervous pathways, by internal secretion, or indirectly through changes in the over-all behavior of the individual. Also, the physiological changes brought about during adaptation to life situations may include release or production of conditioning factors contributory to the occurrence of disease. Hence the association between adaptive reaction and incidence of illness may be explained on reasonable ground. This recognition of the adaptive reaction to a social situation as either a precipitating or perpetuating factor in disease imparts to this relationship an importance in prevention and treatment.

Whatever the explanation, diseases have been produced experimentally as the consequence of adaptation. Similarly, incidence of illness in persons has been associated with life situations conceived by the individual as disturbing and involving the adaptive reaction. In one study it was found that at least one third of all episodes of illness were influenced in their time of occurrence or in their course by the attempts of persons to adapt to situation. From this same investigation came the view that the majority of all occurrences of illness in adults are influenced to some degree by efforts to adapt to the social environment. Hence it has been concluded that man's susceptibility to illness is to a large degree influenced by his relation to society.

This conclusion is not surprising inasmuch as the state of the host has long been recognized to have an influence on the occurrence of illness. Exposure and extreme fatigue are conditions believed to be conducive to the occurrence of disease or to adversely affect its course. Reaction to a disturbing situation surely also represents an altered state of the host.

To carry the sequence of events to completion, it should be stated that not all persons reacting to a situation contract the same type of illness. Just as a similar situation does not affect all persons alike, those who do react with an associated illness do not develop the same disease. Although man's relation to his social environment exerts a major influence on the occurrence and course of illness, it has relatively little influence on the type of the disease. Rather, the type of disease is believed to be determined by various other influences: (1) The physical environment and opportunity for exposure to particular pathogenic agents and conditions extant at that time and previously; (2) the genetic constitution of the person. The variability in these factors could be responsible for the differences in the type of disease developed.

Enumerating a few of the various diseases associated with adaptive reaction, *such as ulcers, colitis, asthma* and cardiac disease, probably brings the word psychosomatic to mind. Actually no qualitative differences have been found between diseases in their relation to social adaptation. Whatever difference may exist appears to be quantitative, that is, certain diseases appear to be more readily and therefore more frequently and more profoundly influenced in their course by the physiological effects of adaptation than are others. These have gained the name psychosomatic diseases.

This account presents a working hypothesis that fits the available observation. It can form the basis for establishing a number of objectives in investigations designed to test the proposition that a relationship exists between social environment, physical environment, genetics, and coronary disease.

Methodology—With this background the group turned to consideration of objectives and the methodology most appropriate for achieving them. Specifically, it discussed the detection of stress and means for measuring its intensity. When it is considered that stress may be induced by a variety of means, that stressors impinge or gain entry to the body at very different points, that in reaction the body uses various systems and processes—physiological, biochemical, and psychological—it is by no means certain that stress is a simple homogeneous quality. Certainly recognition of its possible heterogeneity and complexity gives no encouragement to finding a single test, let alone a quantitative method. It was agreed that stress cannot be directly distinguished. It was admitted therefore that there is no measure of the state of stress per se in the body.

The problem was then approached by considering the relations of stress. One is the reaction to it. Can stress be detected by its effects? This question was discussed in different terms, namely, *the measurement of intensity of stress* by indexes or indicators. Reaction to stress, it will be recalled, comprises numerous functional changes involving physiological processes and behavior.

Some of these changes have been proposed and used as indicators of stress. Changes in metabolic rate, blood pressure, pulse rate, oxygen consumption, blood clotting, mood, or behavior were mentioned. But it was decided that none of these indexes measures stress. Corticoid excretion and blood level were regarded as being more related to stress and therefore better indicators, but their limitations were acknowledged.

It was thought that extensive measurements of these indicators in relation to stress would not be productive. In the opinion of the group there is no simple indicator which provides an objective measure of the intensity of stress. It was pointed out that future research may provide such an indicator. For example, changes in the hypothalamus seem to be close expressions of stress. But a method for evaluating these *changes is not now ready.*

The group then turned to the antecedent relation to stress, namely the factors producing it. A text was cited in which type and load of work were used as indicators in measurement of stress.

Hinkle proposed that a combination of both relations, the antecedent stressor and the subsequent reaction, be studied. Here the stressor was designated the challenge. It was proposed that the challenge be discovered in the constellation of circumstances in the environment, both physical and social, that this challenge be evaluated, and that the reaction to the challenge be studied.

In an investigation of the relation of atherosclerosis and hypertension to personality and the social environment, the complexity of this area and the use of the term "stress" should not obscure the fact that the epidemiological methods here are essentially no different from those used in other medical studies. At the start a hypothesis should be formulated about certain events or processes within the cardiovascular system which are thought to be relevant to atherosclerosis or hypertension and about the way that these processes may be modified by nervous, endocrine or behavioral influences as the individual reacts to his total life situation. As the dependent variable, some measures of the cardiovascular reactions are used. As the independent variable, one can measure objective features of the life situation, features *of the individual which indicate* that he perceives a given situation in a certain manner, or features of the individual (whether socially, culturally, or psychologically determined) which make it likely that he reacts to his life situation in a certain manner. The experimenter counts, classifies, and seeks association, as in any other epidemiological study.

The same considerations of experimental design, selection of sample, and *reliability of indexes that apply in other* studies apply here. The experimenter should try to avoid naive assumptions (such as that primitive societies are less complex and less stressful). He should try to classify like with like (and not to assume that Negro school teachers are the same as Negro laborers). He should try to call phenomena by their precise name (and not to call "anxiety" "stress"). He should try to report results in terms of observations (e.g., responses on a psychological test) rather than as conclusions or diagnoses (e.g., hysterical personalities).

With the help of skilled behavioral and social scientists, specific answers to specific questions can be obtained.

In the same vein Ackerman suggested that the psychosocial representation of stress might be approached operationally in the context of the individual functioning within the family, the family within the community. This approach requires procedures for systematic psychodynamic study of the ongoing interactional processes of the individual patient with his family group. It is assumed that the individual patients would undergo traditional forms of psychiatric and psychological study. Beyond that, however, there would be systematic examination of the family phenomenon, its internal organization and external adaptation to the surrounding community. The individual patient is then viewed as a living unit within that group. Necessary to such an *approach is a dynamic concept of the in*

tegration of personality into required family roles The phenomenon of breakdown and illness may be seen both as a function of the individual organism and as a function of the familial organism Of special significance in this *connection is the relationship between* the emergence of illness and the interplay of individual and family group defense against anxiety

In an attempt to correlate specific *defense operations anxiety and somatic* pathology it is necessary to look into the conflict tension and anxiety aroused by a threat to a person s integrity Perhaps particular configurations of subconscious conflicts and frustrations may be found to be related to disease But the experience of conflict alone is no index of functional breakdown with illness It is essential to note how man perceives a threat in a situation and how he considers which of his resources might be mobilized to protect him and control his tension

Every human being experiences functional distress in a particular way Hence it is no surprise to observe certain reactions in the inner organ system When there can be no release of tension in the voluntary muscles it may flow over into the sympathetic and parasympathetic systems That is an inappropriate kind of mobilization of defense against tension a failing type of mobilization Such inappropriate mobilization suggests that there might be a relationship between *acting out and acting in The phrase* acting out signifies a situation in which a person is experiencing a conflict in a distressing way he cannot cope with it and in an irrational and *inappropriate way* elements of that conflict spill over into society in such a manner as to get him into trouble because his action does not fit the social situation Although the consequences may be unpleasant for the moment the individual has succeeded in relieving the excessive tension and has established an equilibrium for his internal life However it is possible to conceive of a situation in which the individual would like to act out but does not dare Such a situation would elicit different types of defense behavior some indicative of *well being* and some which are pathogenic either psychically or somatically or both It would be profitable to conduct studies on the mobilization of healthy or pathogenic defenses and their *possible relation to disease*

Rather than attempt to work out the sequences of changes in the development of coronary disease with special inquiry into stress Dr Selye would go directly to a study to determine whether substances found experimentally to protect animals from cardiopathy would confer a like protection against coronary disease in man He reported his experimental observations recommending that they be put to clinical test Dr Selye asserted that combined treatment with certain steroid and electrolytes produces a cardiopathy characterized by necroses The steroid was regarded as a conditioning factor i e it conditioned the heart for production of the cardiopathy by the electrolyte Among all steroids tested only certain corticoid had this capacity As a conditioner 2 methyl 9 chlorocortisol (Me Cl COL) possessed the highest potency

Following conditioning of animal with the effective steroid certain electrolytes could induce the necrotic cardiopathy *Only certain sodium salts* specifically monosodium phosphate sodium sulfate and sodium perchlorate had this ability Other sodium salts were inactive It was concluded that both the cation and the anion possessed this sensitizing potency

Certain other electrolytes actually prevented development of the necrotic cardiopathy when they were given simultaneously with sensitizing electrolytes to animal suitably conditioned with steroid Among all the salt

tested pota ium chloride and magne sium chlorid were the most potent protectors

In all experimental animals used—rat guinea pig monkeys and dogs—this reaction has been produced It is fair to as ume at least that a chemical mechanism for it exists in man

Di tinct from the cardiopathy pro duced gradually by the persistent action of corticoids plus certain activating odium salt is the sudden eliciting effect of tre Although pretreatment of rats with thre hold dose of Me Cl COL plus NaH PO_4 produced little or no cardiac damage sub equent expo ure to the stress of neuromuscular effort immediately elicited severe and exten ive cardiac necro es in all experi mental animal Under the same ex perimental conditions of pretreatment, various stre creating maneuvers simi larly induced a high incidence of myo cardial necroses Neither Me Cl COL nor stre s alone produced cardiac ne cro i But after pretreatment with Me Cl COL alone i e without sodium alts numerou quite unrelated agent creating tres had a cardiotoxic effect Hence the eliciting action of stress wa regarded to be nonspecific The pre cipitation of infarct like myocardial lesions by sudden exposure to stressors is of pecial interest in view of its clini cal implications

After pretreatment of rats with Me Cl COL a *ingle intravenous injection* of papain extract produced myocardial necro es more readily than otherwise

It is highly significant that KCl and MgCl are effective in preventing the various forms of cardiopathy produced by the following different means (1) corticoid and sensitizing Na salts (2) corticoid conditioning followed by ex po ure to various tres ors and (3) in travenou injection of a protea e These ob ervation rai e the hope that they may al o be beneficial in preventing cardiopathies in man

It was stated very clearly that the experimentally induced cardiopathies do not reproduce all the histopathologic changes presently regarded as a ine qua non for the development of coro nary di ea e For example there is no athero cle ro is Hence pathologically none of the experimental cardiopathies in animals is an analog of coronary di ease in man

Nevertheless since both potassium chloride and magnesium chloride exert protective action again t various types of myocardial pathology induced experi mentally by different means Dr Selye believes that this fact warrants te ting of their efficacy in preventing coronary thrombosi *in man* *Furthermore* it would be a afe and simple procedure There are three types of procedures commonly u ed in ascertaining etiology and treatment of a disea e (1) experi mental production of the disease u ually in animals (2) test treatment of the naturally occurring di ea e in man and (3) test prevention of the natural di ease If patient studies on the pro tective action of the electrolytes were undertaken the preventive type would provide critical data In addition o many lives might be saved that uch tests are ju tified even if the likelihood of success eems small

Environment Culture

Having considered tress we now *turn to its environmental source* It is obvious that both the physical and social environments may cause stre Becau e the influence of the phy ical en vironment was scheduled to be di cu ed by another section our attention was focused primarily on the social en vironment as a source of stre s Yet o intertwined are the two environ ments that the phy ical environment was mentioned at appropriate points

It mu t be remembered that ociety cannot be considered separately from personality Human behavior i haped

both by the organization of the internal forces of personality and the external forces of society. Indeed the two are interrelated throughout life. Environment has a molding effect on character structure which varies with the distinctive features of each society. At each age level and at each stage of personality organization the environment requires distinct types of social function from the individual. Hence social environment contributes to the shaping of adaptive behavior by determining the path along which the individual may successfully adapt to his surroundings. It reinforces some individual drives and subordinates others. Current factors in the environment influence the social level of personality integration and may even penetrate to the individual personality.

The social environment is also the medium for situations which are the sources of stress. But again the situation cannot be considered separately from the participating personality. The situation derives its meaning from the participant's interpretation. It has been found that a participant in a situation evaluates its stress-provoking quality differently than does a detached observer. It may have a meaning and significance for the participant that does not enter into the observer's evaluation. Hence the problem becomes: How may personalized stress-creating situations in the social environment be detected and identified and how may their relation to cardiovascular disease be studied?

Specialization has brought about a division of the social environment into culture, society, and the family. It is therefore most convenient to consider the nature and methodology of each division separately, yet the three become commingled when any one is subjected to study.

Culture comprises the customs, manners, way of life, and conventional wisdom of the group. This way of life includes innumerable details of behavior which represent the normal anticipated response of any of the society's members to a particular situation. Norms of behavior and opinion constitute a culture pattern. Culture as a whole is a more or less organized aggregate of such patterns. It provides members of any society with an indispensable guide in all the affairs of life. It would be impossible either for them or for society to function effectively without it. It operates with a background of social approval and social pressure.

There are many types of culture in the world. Broadly speaking, they differ in their homogeneity and simplicity. Even within national borders, whether in sections or in smaller subdivisions such as districts, variants of the basic culture may appear. Since the anthropologist in his studies is often concerned with the cultural homogeneity of a sample, he sometimes has to separate population groups into subcultures and even into further fractions. Because of cultural heterogeneity, studies in the United States were regarded as most difficult by the late Ruth Benedict. New York City itself offers an impressive array of subcultures.

Dr. Shapiro emphasized that the most important property of culture is the learned patterns of behavior. By that is meant the patterns that people live by, the expectations they have in the behavior of other people in their own community. These cultural patterns confer the ability to carry on a relatively large series of behavioral patterns in a semiautomatic way. By providing a way of routine living, these patterns spare man the necessity of constant decision. Because once a pattern is established and expectation built up for most of the events in daily life, man can proceed in a predetermined way without giving much thought to it. This proce

dure is of course a saver of time and of emotional wear and tear on the individual for having to make fresh decisions for every item of behavior would indeed be time consuming and enervating Man comes to take his cultural pattern so much for granted that most of the time he does not think about its operation Then when he encounters a situation which is different he thinks of it as being very odd strange and peculiar

No matter how well regulated a society may be how well understood the cultural patterns may be by members of the community there is always a residuum of conflict which may arise anywhere in the social order to provoke emotional stress It was Dr Shapiro s belief that a highly educated society in which the people have a variety of rules and statutes to contend with may contain many more stress-creating situations than does a primitive organization For example being a member of a minority group or exclusion from a social class or operation of economic factors that are flexible and open to manipulation beyond what the cultures might be expected to control—all these things as they appear in the more highly developed society give rise to more situations which could produce stress than occur in a bushman society where there is not much economic distinction between the members of the society where there are no classes and where there are no minority groups Obviously even there some situations which would lead to stress would occur but the number would be fewer

Methodology—It is appropriate to describe briefly the way a cultural anthropologist works his methodological approach, once he has selected his population sample His objective is to provide an account of group behavior in all activities of living But such an area of observation is vast and complex Culture itself has a multitude of component each comprising numerous details To add to the difficulty an individual may differ in his behavior if ever so slightly from time to time and individuals may differ even more from one another Thus a real culture pattern is a series of varying behaviors although the range of variation is usually within moderate limits

This variability of behavior yields data that are much too bulky and unwieldy to be descriptive and workable Hence the anthropologist develops a culture construct pattern by establishing the mode of the series of variations within the effective range of a real culture pattern he then uses this mode as a symbol for the real culture pattern The total culture construct is obtained by combining all the culture construct patterns This procedure provides a concise and convenient approximation of the conditions existing within the real culture It is a serviceable method for summarizing group behavior in the activities of living

It has been repeatedly emphasized that whether a situation is stress provoking depends on the conception of a person involved in it not on the judgment of a detached observer Since the situation thus derives its value from the participant the anthropologist as a detached observer cannot directly unerringly and assuredly detect and identify stress bearing situations At best he can study each culture separately and select those situations that might be stress provoking

Cultural patterns of behavior are the concrete expressions reflecting generalized meanings or values Because of their influence on behavior value orientations play an important function in the lives of individuals Professor Clyde Kluckhohn defines value orientation as a generalized and organized conception influencing behavior of nature of man s place in it of man s relation to man and of the desirable and nondesir

able as they may relate to man environment and interhuman relations.

Florence Kluckhohn has developed a conceptual scheme which will permit a systematic classification of cultural value orientations as they pertain to universal human problems. This scheme sets forth central types of value orientations and the ranges of their possible variability. It is based upon two assumptions. The first is that there is a limited number of basic human problems for which all peoples at all times and in all places have had to find some solution.

Five of these common human problems regarded as being of key importance were stated in the form of questions:

1 What are the innate predispositions of man? That is what is his basic human nature?

2 What is the relation of man to nature?

3 What is the significant time dimension?

4 What is the valued personality type?

5 What is the dominant modality of the relationship of man to other men?

The second assumption underlying the scheme is that solutions found for the problems are variable but that the variability is within a range of possible solutions. She recognizes three types of solution for each universal human problem. This scheme permits a systematic comparison of societies or subgroups on the basis of man's conceptions of fundamental and universal relationships.

Dr Shapiro acknowledged the validity of the types of value orientations. However he believed that their application in observations on individuals might be difficult because they are abstract. As a more useful procedure he prefers to deal with specific everyday situations.

Dr Shapiro enumerated several examples of likely sources of stress in cultures. Mother-in-law avoidance in some American Indian societies is a custom which might be a source of stress whereas in our society with its mother-in-law jokes the situation is not the same. On the other hand social mobility is probably a source of much difficulty in our own society but it does not exist in Polynesia. There the natives are not fired with ambition to become tycoons. Polynesia has no tycoons so the natives have no particular desire to be one. Indeed Polynesia has no social classes and corporations, hence it has no high pressure executives. Prestige and sexual jealousy occur in both cultures but in quite different character. Certainly stress occurs in all societies. What should be underscored is that the origin of the stress may vary not only with the conception of the affected person but also from one society to another. *Even when societies are apparently* similar they may not be because of the different overtones.

Dr Hinkle recounted observations from a cross-cultural study of health patterns in groups of Chinese, Hungarian and American college students. Cultural differences were observed in their attitude toward work, relationship to father and getting ahead. He raised the question whether the type of attitude might be associated with a cardiovascular reaction pattern related to the development of atherosclerosis.

Dr Shapiro pointed out the danger of overgeneralizing on the basis of observations from a subculture. For example getting ahead has a very high value rating among a very limited portion of the Chinese population but it is by no means typical of all Chinese. Nor are all Americans driven by overvaulting ambition and high aspiration. Since there are subcultures in both China and the United States it is risky to use subcultural patterns in making broad generalizations about Chinese and Americans. It is necessary to ascertain how general a pattern is in a culture.

Three other types of studies were re

garded as likely to yield significant information

Because of inadequacies in published data it would be desirable to conduct cross cultural studies on blood pressure

Concerning hypertension it would be useful to study cultural groups in which persons have a desire to act out but fear to do so because of the consequences as contrasted with other cultures in which it is permissible to act out freely

Interrelationship normally provides the individual with some degree of protection In our society this system is not working as well as it might It would be helpful to study groups in which the culture normally provides varied degrees of reinforcement The individual should be studied in relation to the family and to the larger culture In this comparison of cultures possible relationships with cardiovascular disease should be tested

To Dr Shapiro the paramount question in methodology was how to evaluate stress in one culture in comparison with stress in another It is a difficult problem because the personal reaction appears to outweigh the particular situation For example is the Chinese boy striving for scholastic prestige under the same kind of tension and pressure as an American youth attempting to climb in a business organization? It is conceivable that the two situations require different types of adaptation Whether one might be associated with a significant change in cardiovascular function is a matter for testing Above all it would be helpful to have an objective physiological measure for evaluating the stress provoking potency of situations Then they could be more readily identified and compared in different cultures

Some caution should be exercised in the consideration of broad cultural factors associated with stress as possibly related to heart disease Specifically the following conceptions and practices are to be avoided

1 Lumping all threats or strain upon the individual under the encompassing term of load stress or challenge It would be better in any anthropological investigations to make observations on more limited and specific phenomena i e fear rage dilemmas of decision ordeals of endurance or tolerance

2 Failure to differentiate as far as possible between the phenomenon of culture and the phenomenon of society For research purposes there is an advantage in keeping them conceptually and somewhat operationally separate

3 The popular and largely false assumption that the relatively primitive and preliterate societies are simpler and less stressful than are our sophisticated and civilized societies Their stressors may be more intense than ours and some of their components may be more complex (language kinship systems and so forth) We can be certain of finding wider cultural contrasts in primitive societies but not so certain of finding greater simplicity of components or potential stressors for personal experience

4 The easy assumption that culture and society are primarily offenders rather than befrienders to persons subjected to stress (fear etc) The primary function of culture and society is to solve or resolve a people s problem Most sociocultural systems do a reasonably adequate job of it

5 A tendency to neglect or ignore the utility of a balance between stress induction and stress reduction mechanisms within a sociocultural system (ghost fear)

6 Failure to properly differentiate between a homogeneous and stable culture and a heterogeneous and/or changing culture There is an apparent tendency for the reduction mechanisms of culturally induced stress to break down more rapidly than the induction mechanisms

7 Failure to recognize and account for the fact that culturally induced stress is subject to modification by the significant reference group members and

by individualized personal experience (family).

8. Failure to allow for or to take advantage of the phenomena of cultural selectivity in socially conditioned stress induction and stress reduction.

9. Possible lack of adequate recognition and utilization of existing sociocultural variation in family size and structure.

10. Possible lack of recognition of the research potentials of cultural variation for testing the hypothesis of "acting out" and "acting in" of stress frustration.

Environment Society

Concurring in the statement that no societies are free from sources of stress, Professor Simmons went even further in saying that it probably would not be possible for a society to survive without sources of stress. As society's means to stimulate and control action, stress has a survival function. Professor Simmons described a procedure for identifying stress-provoking situations by "peeling off" layers of perceptive interpretations of them. A list of critical situations with a potential of creating stress in the life of man in his culture is prepared for a particular society. Three questions are then applied to each situation: Would it induce stress because of its physical elements? Is its stress-inducing nature reasonable only in the light of the culture? Is there any aspect of the situation provoking stress that is not explainable by either the physical environment or human culture and dependent upon the special experience and idiosyncrasies of the participating individual? In short, these questions seek to ascertain whether the stress-inducing nature of the situation has a basis of physical or cultural realism as shared by other members of the society.

When applied to the Hopi Indian, it was surprising to find little in the physical environment that served as a real istic source of stress. Yet it was obvious that in their lives the natives experienced much stress, mostly cultural in origin. Certain situations also had stress-productive aspects that did not seem to make sense. Deeper investigation revealed that the natives had been conditioned to fear particular situations. It was then possible to place much of the seemingly illogical and unintelligible in the category of culturally realistic stress-bearing situation. Furthermore, it was observed that although the natives are subjected to culturally determined stress potential, their stress is resolved by other cultural provisions. Thus the culture creates stress-provoking situations *but it also provides protective measures against them*.

From these observations, Professor Simmons concluded that it is necessary to look searchingly into both the culture and the person's life history to discover what patterns conditioned his fear. It may be necessary to slice the culture into such subcultures as occupational, ethnic, religious, and familial aspects in a given society.

The usefulness of social variables in society for epidemiological studies might be considered on the basis of their possible relevance to stress or cardiovascular disease, e.g., the nature of the social system, social status with process of social stratification, social interaction, and social mobility, and social roles whether they be ascribed, achieved, adopted, or assumed.

Other sociological variables used in various studies and found to be significant are social class, type of residential area, occupation, identification in the general population, authority, leadership, responsibility, and affectional ties. To these may be added the following variables: size of group, forms of internal communication, rules determining rights of members, method of assigning tasks, and handling grievances.

A program of sociological research

into the epidemiological factors possibly associated with cardiovascular diseases might profitably follow the plan which is outlined by Dr Simmons with steps taken somewhat in the order named If undertaken by sociologists it should be under the constant counsel *and guidance of a medical team of per*sons who are recognized as experts in cardiovascular disorders

A general ecological approach would be recommended as preferable particularly in the initial stages of the study Study should be concentrated on a particular geographic area containing a reasonably wide range of factors suspected to be significant in predisposing persons to cardiovascular disease In addition the factors considered (biological social cultural familial psychological etc) should be those for which fairly reliable techniques of differentiation and/or measurement are available It would also be preferred that an area where a considerable number of good ecological studies have already been made be chosen in order to take advantage of the accumulated ecological knowl*edge existing on the area Good examples* would be New Haven Conn Providence R I Framingham Mass or Evans County Ga Other areas might be selected later to serve as areal controls or for comparative purposes The chosen area should be sufficiently representative to make possible the gathering of data on the various factors listed below or at least a selection of them

A representative sample should be taken of the entire population of the area as of a specified date This sample would serve as the base line and population from which all the succeeding data would be drawn for analysis and correlative test

Every member of this sample (with provision for substituting members for drop outs or those failing to cooperate) should be subjected to a competent medical diagnosis to determine the presence of cardiovascular disease both in clear cut instances when there is no doubt of the actual presence of the disease and in cases of border line incipient or potential existence of the disorder Others should be medically identified as clearly free of any recognized symptoms or in*dications of incurring the disease* These would serve as controls or for panel or cohort studies in long term perspective The ill and potentially ill would be classified according to degree or type of complication age and other categories to be studied as the research progressed Probably special attention would be given to the middle aged and younger categories and only general attention paid to the aged persons

Some order of priority or sequence should be established in the making of statistical checks on incidence or prevalence of the disorders as correlated with existing social factors. An order such as the following might be followed sex racial or ethnic grouping rural or urban residence ecological areal placement in the region studied immigrant generation religious affiliation social *class position as specifically or opera*tionally defined—family structure stability and status as operationally defined extent of social mobility a operationally defined etc

When these gross statistical correlation have been carried as far as feasible on the basis of findings intensive interviewing of stratified sampled and perhaps paired respondents should begin for much more detailed and definitive studies These could be made on a one shot cross sectional basis and on a long term periodic panel basis Such factors as shifting age status economic stability family equilibrium social mobility diet stress components and so forth could then be studied in the context of case history and life history as well as the sociological context

This is perhaps as far as it is at all useful to suggest possible design for an

ecological study. Next steps all along the way would be influenced primarily by the findings from the steps previously taken.

Environment: Family

In the vast social structure a key unit is the family. It is a primary group intermediate between the individual and wider society. Here in this smallest and closest social group culture, society, and the genes meet. Family bonds are made up of a fusion of factors: biological, psychological, social, and economic. The family has a natural life history of its own; on the other hand, every person in his lifetime has several different families, one for each period of his life.

Among the number of social purposes that the family serves, two will be particularly mentioned: (1) It determines *the forms of behavior that are required* in the fundamental and prominent roles within it, and (2) it provides training toward integration into a wide range of social roles and acceptance of social responsibility. Specifically, family relationship *controls the quality, quantity,* and direction of emotional expression; it regulates and patterns the form and range of opportunities for security, pleasure, and self realization; it develops a sense of responsibility for the welfare of others; it teaches evaluation of unexpected danger in a situation; it intensifies or lessens anxiety; and it influences the choice of defenses against it.

Obviously, to fulfill these purposes stability of the family is important. The stability of the family and its members hinges on a delicate pattern of emotional balance and interchange. The behavior of each member is affected by every other member. The degree of stability in family relationship is the end product of complex interdependent processes, for it is governed by the interaction of family members in their respective family roles. One requirement for stability is maintenance of continuity of identity. Against this are balanced the requirements of capacity to change through receptivity to new experience and learning, to achieve further development and to fill new life roles. Effective adaptation requires a favorable balance between this protection of continuity and accommodation to change. The homeostasis of behavior—the balance between continuity and change, the clinging to the old and receptivity to the new—is influenced in turn by the capacity to cope with conflict. Operating to prevent a conflict, to establish a protective equilibrium, *or to compensate for conflictual* effects is the pattern of family role relations called complementarity. Failure to find an effective solution for control of conflict leads to adaptive breakdown which engulfs all members of the family.

Through faulty functioning the family may become a source of stress or fail in its support of a member already under pressure outside the home. When a family becomes disabled and its operations impaired, its stability is threatened. *Usually such impairment in performance* is not total but partial. Some components of family functioning maintain their integrity while others are disabled. Families exhibiting deterioration may be thought as of progressively failing to carry out their essential family function. Ackerman has devised a system of grading families which expresses quantitatively the extent of their disability.

Breakdown in the psychological operations of the family group does not occur all at once. Initially it may be relatively localized and may be manifested in impairment of the family's capacity for problem solving and decision making. In the beginning the disintegrative effects of breakdown may be relatively subtle, but by degrees they spread progressively to affect more and more of the family's basic functions. At this point manifestations of breakdown

disorganization are so unmistakable as to be easily detectable isolation of family members critical barriers to communication conflict and hostility disintegrating family unity With these developments the family as a group can no longer fulfill even its minimum functions

During the course of deterioration efforts may be exerted to halt or reverse it Families vary in their capacity to contain those problems for which they cannot find a solution while endeavoring to make some tolerable restitution Such compensatory behavior is possible only when despite conflict and alienation some family pairs are able to maintain a satisfying pattern of complementarity In one way they may damage one another yet in another they may provide material support and satisfaction of mutual needs

Not to be overlooked is the relationship between family conflict and psychological conflicts within a member This relationship is a basic influence on both individual and family stability for the stability of the individual personality is partly dependent upon the stability of the family Here again complementarity in family role relations fundamentally influences the course and outcome of personal conflict

Stress in the family has focal points that are readily recognizable As a group the family develops a major pattern in its difficulties In some the major area of stress centers in the marital relations in others in parent child relations in still others in the struggle to reconcile the requirements of multiple roles or to establish the position of the family in the wider community Stress and conflict emerge when the behavior of a member in one family role fails to complement the needs of the member in the reciprocal role

Methodology—It is difficult to correlate culture or personality with either stress or somatic illness unless the reference group is also interpreted for most influences upon the individual are registered through the intervening network of interpersonal relations The family is one of the most influential groups Accordingly the individual should be studied not in isolation but within the framework of his ongoing experience and interchange with the family group In that context personality and life histories of individuals may be studied in relation to stress and somatic illness

In an examination of the family in its relation to stress and somatic illness it is clear that all elements must be included the individuals the family group and the various interrelationships In particular this examination should cover the following areas each member's personality his interactions both within his family group and outside with the wider social unit the internal organization of the family it performance of functions which influence each member by inculcating both family roles and the social responsibility which comes with wider social roles and the external adaptation of the family to the surrounding community

When a person conceives of a situation as disturbing or threatening he reacts with tension and anxiety In this circumstance he considers which of his resources may be mobilized to protect him and to allay his anxiety In order to understand the personalized disturbing element in the situation and the individual's reaction to it it is necessary to look into the individual's personality conditioning and defenses But the individual is an interacting member of his group hence it is essential to study him and his life in the context of his group

In a study of the family as the related group certain points should be observed major areas of stress presence of conflict state of stability or deteri

oration performance of basic functions especially support of a member who may have anxiety, and interplay of individual and family group defenses against anxiety It is necessary to measure the extent of psychic resources for control of anxiety both in the individual and in the family group and to correlate the defense behavior of the *individual with that of the network* of close relationships since the latter composite plays an essential part in the mobilization of defense against the effects of anxiety Somatic breakdown is related to the success or failure of these defense operations In fact it is impressive to note the apparent cor*relation between crises in somatic func*tioning and the release of acute anxiety because defenses break down Thus when the individual is studied within the family group it is possible to relate the occurrence of illness to an episode of anxiety and to breakdown of defenses

Ackerman has developed a method of examining the family and has published a detailed guide for it application * His examination include the following behavior components the relative autonomy of the individual his emotional integration into family group *that is the adaptation of his personality* to the required family roles the fit or lack of fit for the same individual of significant familial or extrafamilial role the extent to which the reciprocal role behavior of other family members support or threaten the stability of the individual and the psychological identity and value orientation of the family group and its external adaptation to the community Data obtained on these points provide the basis for determining the nature of three interrelated sets of processes (1) What goes on inside the individual (2) what goes on between this individual and other significant family members and (3) psychosocial patterns of the family as a whole

Several reported investigations on illness in relation to the family have concentrated on one or another aspect of family life e g the role of cultural values *situations of crisi*

The Individual His Personality and Psychological Reactions

We now return from the environment to the individual and his susceptibility to both stress and heart disease It has been postulated that certain individuals are more vulnerable to stress of these a certain number appear to be prone to develop coronary disease or its circulatory precursor For two reason this subject has practical significance (1) the elucidation of factors responsible for the development or precipitation of heart disease and (2) the ability to predict the probability of the occurrence of heart disease and to make early identification of probable victim as a basis of prevention

Vulnerability to stress and vulnerability to coronary disease are two different characteristics yet because of their possibly significant association they may profitably be studied either separately or jointly A person s relation to stress exhibits two aspect (1) his sensitivity to stress i e the appropriateness frequency and intensity with which a person conceives of situations as disturbing and (2) the nature of his reaction to that stress It is possible that a particular type of reaction to stress may be one of the factor influencing the occurrence or course of heart disease Such a sequence would explain in part any vulnerability to the cardiac complex

Is there a particular personality type associated with development of heart

* Ackerman N W *Life Stress and Bodily* Disease Character Structure in Hypertensive Persons Res Publ Ass Nerv & Ment Dis 29 900-918 Baltimore Md Williams & Wilkins 1950

di ease? What are the characteri tics of such an individual? These seemingly simple questions open a very large and complex area The meaning of per onality itself has been an elusive ub ject Allport has compiled more than 55 definitions of personality which have been propo ed at one time or another Since the method of distinguishing per onality types depends upon conception of the nature of personality it is theo retically po sible to have a different method for every definition

Actually four tudies have reported on personality type and heart disease or ome a sociated sign such as hyper tension U ually these tudies were conducted after signs had developed Accordingly the significance of the re ported observations has been questioned Did the observed per onality pattern precede or follow the occurrence of coronary disease or hypertension? Or did the same factor or et of factors that produced heart di ea e also bring about the per onality change? It may be said at this point that investigators believe that the personality structure has been laid down long before the appearance of heart di ease

It will be recalled that Wolff and Hinkle found that whether a situation is capable of inciting stress in a person depends upon his perception of the ituation its meaning and its value for him This point of view is in harmony with the possible vulnerability of an individual to stress

After reviewing those ob ervations and conclusions which bear upon the topic of vulnerability and characteristics of the vulnerable Dr Hinkle propo ed a type of procedure to obtain further knowledge People differ in their su ceptibility to illness regardless of its nature Tho e who became ill most frequently were found to be more likely to develop both more varied illne es and more evere illnesses than tho e who became ill le s frequently All type of illness seemed to occur ome what more frequently during period when the individual was having diffi culty in adapting to the total configura tion of his life It is to be expected that a man s adaptive reaction pattern will exhibit a variety of alteration depending upon his own constitution previous conditioning and the circum tances he encounters Con equently it it understandable that he would develop a variety of illnesses

It is rea onable to assume that cardio vascular di ea e might be among the di orders arising out of man s inter relation with his environment As he goes through life man might have an adaptive reaction pattern that i re flected in the function of his cardio va cular system and if continued over a sufficient period of time this pattern might produce disease Thus men de veloping cardiac pathology will not nec e sarily be different from those con tracting other illnesses except po sibly in one or two characteristics of the specific adaptive reaction pattern rele vant to the cardiovascular system

Hinkle pointed to the need to find out more about the characteristic both physiological and psychological of per sons with cardiac di order and their reactions to ituations More specifically he proposed trying to identify (1) the nature of the challenge in the situation (2) any peculiarity in the evaluation and (3) the nature of the cardiovascular reaction pattern He pointed out the desirability of taking general hypo the e developed on evidence from the laboratory out into the field Unfortu nately in atherosclerosis and heart di ea e the laboratory evidence on which hypothese may be built is quite limited Possibly the best hypotheses at hand were derived from limited laboratory ob ervations on persons placed in rela tively acute situations to which they responded In these tudies mea ure ments were made over a rather hort

period of time on a limited number of variables.

One such hypothesis would be: In short term experiments persons may be subjected to situations which are designed to threaten them. As part of their reaction some of them will develop elevation of blood pressure. Some persons perceiving their life situations as threatening to them also exhibit an adaptative reaction which includes an increase in peripheral resistance with elevation of their blood pressure. If this adaptative reaction were carried on over a long period of time it might ultimately produce hypertensive cardiovascular disease.

How does one identify persons who are prone to this type of reaction? A proportion of the people who react in this way seem to have a singular mental pattern which makes them easily threatened by a variety of circumstances. They react to this situation with an aggressive feeling which they have difficulty in expressing.

Not all of these persons necessarily have anything abnormal about their cardiovascular apparatus. Many people in the population who have this personality trait do not have hypertension. On the other hand a significant number of hypertensives do not have this trait. Nevertheless it is probable that this trait occurs more frequently in hypertensive.

One way to test this hypothesis would be to study cardiac morbidity rates in populations which differ in their conception of certain threatening circumstances, i.e. whether they see them else as threatened. For this it is necessary to turn to the anthropologist. It is a reasonable assumption that certain societies facilitate in their members ready expression of the aggressive response elicited by such threat while other societies hinder it. Some people are in a situation in which their treatment by society is likely to arouse in them a great deal of hostile resistance which they cannot express because that would only make the situation worse.

Another hypothesis may be cited: When certain people are faced in life with situations that they regard as threatening the biologic response will include a significant rise in the blood cholesterol. If this metabolic reaction pattern is sustained over a period of time it is conceivable that it facilitates the development of atherosclerosis.

In a certain number of people this type of adaptative reaction is associated with mobilization. This raises the possibility that it is the striving member of our society who are particularly susceptible, those who get up earlier, work harder and longer, and keep going all the time.

To test this thesis again we turn to the anthropologists to identify societies in which this pattern seems to be prevalent and other societies in which it is not.

From studies over a number of years of the personality characteristic of hypertensive patient, Ackerman has developed a hypothesis. In evaluating the character structure of these patients he has placed special emphasis on their defense behavior and role adaptation. They exhibit, he has noted, a pyramiding series of specific shock reaction in the personality representing the responses to experiences conveying real or symbolic threat. In these reaction the processes for control of emotion are acutely overwhelmed and the adaptive functions of the personality undergo impairment or breakdown. Specifically the defense mechanism of repression proves inadequate; auxiliary defenses which are then mobilized also are insufficient. With this paralysis of the adaptive processes a state of temporary emotional disorganization is induced. There is a loss of balance in the integrative functions of the personality at all levels. This inadequacy is reflected in

the failure to maintain a characteristic social role which is significant in the preservation of security in interpersonal relations It is assumed that the potentiality for this particular form of shock reaction depends on the specific pattern of emotional predisposition conditioned by the vicissitudes of experiences during the formative stages of personality Thus there is believed to be a basic factor of vulnerability in the personality which long antedates the emergence of overt symptoms of hypertension

The generalized impairment of adaptive capacities in this shock reaction is transitory The loss of emotional control while profound is brief equilibrium is quickly restored After a series of such critical episodes precipitated by traumatic life experiences which symbolically spell a danger the presence of hypertension is often revealed Its onset is associated with a pyramiding series of specific shock reactions in the personality In the later stage fixation of the distortions of adaptive function of the personality is seen involving increasing rigidity of the psychophysical mechanism of the personality The component of conflict which is primarily related to the hypertensive reaction is that which occurs between the person and the environment rather than the person's conflict with self In sum it is believed that a preexisting vulnerability in personality plus the reactions to traumatic life experience produce the condition in which blood pressure is elevated at first reversibly later permanently

From his study of hypertensive person Ackerman has gained impressions of their personality Their behavior suggests that they would like to act out and to behave like psychopaths but do not dare

Acting out signifies a situation in which a person is experiencing a conflict which causes him distress and which he cannot cope with in a rational and appropriate way Thus his manner of resolving this conflict is likely to get him into trouble because his action does not fit the social situation From that action unpleasant consequences may ensue but for the moment the individual has succeeded in relieving the excessive tension and has established an equilibrium for his internal life

The behavior of a psychopathic personality illustrates acting out He is a highly egocentric person who is antisocial gets into trouble with his surrounding social group is against everything laid down by prescribed social behavior defies tradition and gets into trouble with the law The psychopath acts as if he were more powerful than the forces of his environment He acts senselessly as if he had some magical power to make himself stronger than anyone else in his social group

In characterizing the personality of the hypertensive patient as a would be psychopath Ackerman stated that such a person is motivated in phantasy by a desire to live like a psychopath But he does not dare The fear of retaliation is overwhelming So he does not have the ability to master the environment with hostile aggressive power On the other hand he is not able to accept and execute a role of submission to and dependence on the environment Obviously the two roles are incongruous and irreconcilable That is his dilemma

Hence he acts in It is no surprise to observe reactions in the inner organ system When tension cannot be released in the voluntary muscles it may flow over into the sympathetic and parasympathetic systems It is however an inappropriate failing type of mobilization of defense against tension

Ackerman has explained the psychological processes underlying this behavior One prominent manifestation in a hypertensive person is the overtense conflict experienced in the effort to control aggressive impulses and the ten

dency to suppress the translation of such impulses into action. Suppression occurs because the usual defenses are unsuitable and defective. Attempts to cope with impulses through repression are unsuccessful and auxiliary defenses also are inadequate. It is not clear that this pattern of defective repression is specific for hypertension; it may prove to be a common pattern in a variety of psychosomatic disorders. Conscious suppression of emotion represents the final defense against the threat of loss of control. If the basic impulses were to break through the control mechanisms and be discharged into action, it is likely that the resulting behavior would be either psychopathic or psychotic. When psychosomatic phenomena appear instead, it is believed that they represent a substitute for a break through of emotional control with direct translation of impulse into action.

The component of conflict which is critical in the hypertensive phenomenon and possibly in other psychosomatic disorders as well is that which takes place largely at the level of translation of conscious or preconscious emotional experience into action, i.e., the level at which the patient struggles with some degree of consciousness to act against the presumed dangers of the environment. The patient's reaction reflects a strenuous effort to control or even actively reshape the environment whether at the level of reality or at the level of omnipotent mastery. The implied urge is to mobilize magic power in order to coerce significant persons into a protective and supportive role. It therefore seems that the externalized rather than the internalized component of conflict is *specific and crucial* for hypertensives.

In the process of adaptation, social role may represent either a positive expression of *individuality* that is, role and personality may coincide, or a negative function of defense. In the latter case the effort to execute a particular social role may exact an excessive price in the terms of conflict and anxiety within the individual. Or the inner conflict may be such as to damage or actually prevent the execution of a given social role.

The relative success or failure of adaptation in the context of a given role is partly the result of coincidence or conflict between a particular character disposition and a particular group environment with its status and role.

For these reasons the relations between personality and environment have much significance in the development of hypertension. It would appear that the link between emotional reactivity and the hypertensive response, i.e., psychological specificity, is to be sought, not in the content of conflicting drive nor in the total personality configuration, but rather in the specific pattern of defect of the mechanism of control *of emotion in a situation of undue stress* between the person and the environment. All that has been said suggests a focus of interest on the structure of the social environment and on the ego regulatory mechanisms of personality in hypertensives, especially the precise defenses which they employ against impulse discharge and anxiety. Accordingly, any psychological specificity is to be sought in those mechanisms of the hypertensive person which integrate emotion and control translation of impulse into action in the performance of a social role. In short, the emphasis is on role adaptation and defense behavior.

It thus becomes necessary to ascertain (1) the particular ego integration patterns and defenses employed in a given role, (2) the degree of adaptive efficacy or failure, (3) the manner in which such defenses are periodically overwhelmed, (4) what forms of compensatory defense are erected in the phase of recuperation following a temporary break through of emotional control.

To obtain this information in testing the validity of the hypothesis the usual psychoanalytic approach is inadequate It does not provide a sufficiently accurate cross section appreciation of total character in particular those patterns of character integration that in a given time and given environment are projected into a given social role Actually psychoanalysis is not oriented toward examining the social self Rather it has tended to emphasize a denuding by the patient of the social layers of his identity in order to gain access to the unconscious and biologically conditioned drives Thus it keeps in abeyance the very ego integration that would be a principal object of study in hypertensive persons

Ackerman has devised a guide for the evaluation of total personality function in the context of the present time and the present life situation It stresses pattern of ego integration oriented to the maintenance of a given social role or role in a given environment He emphasize that the personality should not be disassociated from the environment Rather the two should be treated as a functional entity The picture of the patient s personality should be unified and dynamic and his functional relation with his environment should be preserved Ackerman suggests that this mode of analysis might profitably be applied to a larger group of hypertensives

Professor Carney Landis offered still another approach to determining the characteristics of person who develop cardiac disease He pointed out that most scientific discoveries have resulted from someone s asking the right question For effective results from direct interrogation a set of relevant questions must be designed for the occasion If he were to undertake such a type of study on cardiac disease he would first obtain from a number of cardiologists what they thought were the relevant questions Then he would design the interview

The biggest obstacle to such an inquiry by direct questioning is the scarcity of suitable interviewers It should be strongly stated that interviewing cannot be turned over to unskillful and untrained persons It takes a long time to find and train competent interviewers

In order to discover the characteristics of persons vulnerable to heart disease Professor Landis would question two groups (1) persons with undoubted hypertension and (2) those who had had a coronary attack He would ask them pertinent question to find what their life experience psychological problems and social relationships have been

To the protest that many coronary patients could not or would not submit to an interview Professor Landis maintained that any question can be asked if it is asked in the right way and under the proper circumstances and it will be answered

He recommended that the application of any tests should come only after completion of the survey by interview never before Only after the relevance of questions in the interview has been confirmed is it possible to prepare tests for the investigator must apply tests that are relevant to the intended use In his opinion there is no available psychological test which has any relevance and therefore any primary value in cardiovascular disease On these ground he would not apply the Army Alpha Rohrschach or Thematic Apperception Tests Nevertheless he thinks that after the survey by interview has indicated the pertinent questions it should be possible to design tests with the requisite relevancy for cardiovascular disease

Worth noting is Professor Landis estimate that to properly conduct a study by direct questioning would require 15 years

Genetics

At the outset of consideration of genetics in relation to heart disease two

points should be kept clearly and emphatically in mind. In a sense they are the present day doctrines of genetics. One principle is that what is inherited for the most part is a potentiality, not an inevitability. Whether this potentiality develops into an actuality depends primarily upon environmental circumstances. Thus genes do not exert an absolute control but determine potential development in particular environmental situations. The second principle, which is really a corollary of the first, recognizes that genes and environment are interrelated; that an interlocking network of hereditary and environmental influences determine the outcome.

Conceivably genetics may influence in several different ways the development of coronary disease; it may act structurally or functionally at various stages of pathogenesis. This possibility raises a number of questions for investigation. In general the numerous relations and questions concerning them may be grouped in three major categories.

The paramount question goes right to the crux of the matter: Is there a hereditary predisposition to coronary disease? To answer this question requires a direct over-all approach which does not necessarily cast any light on the mode of relationship. But its answer would provide fundamental information which would have practical application in the prevention of heart disease.

Aside from its value per se the answer might dovetail with knowledge of specific points in the hypothesis of the sequence in pathogenesis. Determination of whether there is a vulnerability to cardiac disease for which genetics has at least a share of the responsibility might complement existing partial evidence on the sequence of events in pathogenesis; in consequence to that extent it might place the hypothesis and its parts on a more substantial footing. Out of the group of persons with an adaptive reaction leading to frequent illness from a variety of diseases, why do only some persons contract heart disease? What is the basis of this selectivity? To answer this question it is important to find out whether certain persons inherit a potentiality for developing coronary disease. Surely it would also stimulate a number of investigations on specific points. For the over-all approach available methods such as study of hereditary lines or twins are well known.

The second large question concerns the possible distinctiveness of persons who will develop coronary disease and the genetic transmission of this quality. Can such individuals be characterized in a prototype? Are there recognizably distinctive characteristics associated with a person who tends to develop coronary disorder? Are these features transmissible? Demonstration of an association between a distinctive type of person and his vulnerability to heart disease raises the question whether his characteristics have any hereditary basis.

There have been a number of efforts to type persons who develop or have coronary disease, for valid typing would be extremely useful. It would provide an index for identifying potential coronary victims so that preventive measures might be instituted. Furthermore, although typical characteristics might not explain the pathogenesis of heart disease, they might furnish a clue to the significant features of the process. If the characteristics were found to be under genetic influence, the usefulness of typing would be enhanced on both scores.

For present purposes it is desirable to know whether well defined, easily recognizable characteristics validly significant and specific for coronary disease are available for use in genetic studies. Attempts have been directed at two bases of distinguishing persons: body type and personality. Gertler and White have re-

ported that coronary disease occurs more frequently in persons with endomorphic mesomorph body build. Technics of physical measurements and a number of systems of classification of body type were developed long ago. The selection of significant physical measurements and the validity of the systems of classification have been the objects of critical comment and difference of opinion.

Four studies have been conducted on the personality type associated with persons having hypertension. Briefly stated, the present attitude is that it is less promising and less profitable to establish personality type associated with coronary disorder than to investigate the psychological reactions, especially role adaptation and defense behavior, of persons who develop hypertension and coronary disease.

The third area of investigation by genetics has to do with the various pathological changes in heart disease suggested, reputed, or demonstrated to be under genetic influence. They may be arranged in four groups: psychological, physiological, biochemical, and histological. At one time or another eight different changes have been speculatively associated with genetic influence. It is to be borne in mind that for the most part the relation of these changes to genetics is at present a postulation. These changes are shown in the following tabulation:

Psychological	Biochemical
Role adaptation and defense behavior	Hypercholesteremia Lipoprotein Blood coagulation
Physiological	**Histological**
Vascular hyperactivity Transient hypertension and tachycardia	Arterial wall width Defect at junction of intima and media

From examination of this tabulation it is obvious that genetics may be related to three level of cardiac disease according to the nature of the pathology: structural, functional, and metabolic. Hence genetic methods must be applied in conjunction with morphological, physiological, and biochemical technics.

Only four changes were considered in detail by the group: adaptive reaction, a lesion at the junction of the intima and media in the coronary artery, lipoprotein, and blood coagulation.

Why some persons react to stress with illness but why only certain of these develop cardiovascular diseases are questions usually explained by attributing this selectivity in part at least to genetic influences. These questions make pertinent the investigation of the possible relationship of two separate phenomena to genetics. One of these phenomena—namely genetic influence in the selection of the heart as the vulnerable point—has already been discussed.

Now the nonspecific adaptive reaction comes under consideration. Here the objective is to ascertain whether the adaptive reaction and its apparent responsibility for vulnerability to illness as indicated by the frequency with which it is associated with illness in particular individual is determined at least in part by genetic processes. For present purposes vulnerability to illness is of interest only in so far as it indicates the type of adaptive reaction that is responsible. It is assumed that this reaction could lead to cardiovascular diseases or any of a number of others depending on different factor. As such it may be regarded presumptively as one stage in the pathogenesis of cardiovascular disease. If this type of adaptive reaction is conducive nonspecifically to heart disease, it is important to ascertain whether this reaction has a genetic basis, i.e. whether certain persons inherit a potentiality for developing it. But to establish a genetic relation to any characteristic one must have a reliable means of identifying that distinctive feature. At present there is no quick and sure

means of accomplishing this identification. Hence application of a genetic approach awaits perfection of an identifying method.

Next to be considered were the processes relevant to the development of atherosclerosis and thrombosis and conceivably affected by genetic influence. In describing the formation of the atherosclerotic plaque, Dr. Wilkinson pointed out that two theories have been proposed to explain the origin of the early deposit. One postulation is that there are always circulating in the blood tiny thrombi which may attach themselves to the vessel wall; one does attach itself and starts to organize; during the process of organization fatty infiltration and calcification occur. The second postulation about the process of atherogenesis is called the infiltration theory; has wider acceptance on this continent. According to this theory there is a constant flow of fatty particles from the inside to the outside of the vessel. But for some reason in atherogenesis infiltration builds up at the junction of the intima and media of the coronary artery and lipid material collects to constitute a formation. In composition this material at first closely resembles the circulating lipids of the blood, i.e., the lipoproteins. As the lipid infiltration ages its composition changes: relatively more cholesterol and less of the other lipids are present. If this infiltration progresses it becomes a yellow or lipid plaque. As this lipid plaque ages, scarring and calcification may occur until very little lipid material is left. The resulting pearly plaque is composed of fibrous tissue and calcium.

Atherosclerosis is widely prevalent; most adults are found to exhibit it. In the two sexes there is probably no difference in the total amount, but there is a difference in distribution. In the male the coronary artery is more frequently involved; in the female it is seldom affected until after the menopause. It is postulated that atherogenesis in the coronary artery is associated with an inherent defect at the junction of the intima and media and that this defect is an inherited characteristic.

Despite the widespread prevalence of atherosclerosis it is only when a complication such as the formation of a thrombus on the eroded surface of the plaque sets in that clinical disease may be said to have occurred. For this reason the amount of atherosclerosis is not so important as the chance distribution of it.

Various factors influence atherogenesis. The rate and manner of formation of the plaque is affected by primary and secondary factors. Age and sex are primary factors. With age there is a tendency toward increased atherogenesis. Quite apart from the effect due to hormonal differences are the anatomical effects of sex on atherogenesis. At birth differences may be distinguished between male and female coronary arteries, both in thickness and in anatomical configuration in the heart. These primary factors favoring the female would probably account for from 2 to 3 per cent of the difference in death rate for coronary disease between males and females if there were no secondary factor.

Among the secondary factors affecting atherogenesis may be mentioned hypertension, diabetes, renal disease, hypothyroidism, hyperlipemia and hypercholesteremia. Hypertension is probably the most important factor in the list. Of the remaining factors, hyperlipemia is of special note because of its relation to the clinical disorders. In effect those metabolic diseases that increase the rate of atherogenesis remove the female sex protection. For example, female diabetics at any age are just as likely as nondiabetic males to have atherosclerosis. The one common denominator in the metabolic condition that removes the female sex protection is a secondary hyperlipemia.

Genetically determined hyperlipemia appears to be indistinguishable from secondary hyperlipemia With the hope of comparing within family groups the effect of hyperlipemia nine genetic types have been postulated In setting up genetic studies it is important to *find the carrier state Hyperlipemia is* noticeable in the homozygous It may also be observable in the heterozygous individual by the time he is 30 Dr Wilkinson emphasized that if every person between the age of 25 and 35 merely had his blood inspected and his *diet adjusted if he were found to have* hyperlipemia from 3 to 10 per cent of potentially fatal coronary diseases could be prevented When all the possible secondary factors in the development of the atherosclerotic heart are studied it may be that some of them will be found to be just *as important as hyperlipemia* or even more so

Medical genetics is in the midst of an extraordinarily active and fertile period largely the outcome of investigations into the biochemical backgrounds of disease Accordingly Dr Block presented *the biochemical approach* to genetics with special consideration of lipoprotein patterns and heart disease Before indicating promising lines of investigation he reviewed the biochemistry transport and intermediary metabolism of lipoprotein

Total lipid in the blood comprise neutral fat cholesterol cholesterol ester and phospholipid In the blood stream these lipids are carried in combination with protein These lipoprotein make up from 12 to 15 per cent of the total protein in normal human plasma Serum *protein itself* is composed of two heterogeneous groups of proteins—albumins and globulins—but it may be further fractionated Electrophoretic analysis of serum protein yields a diagram containing five *to ten protein boundaries* depending on the type of fractionation Each boundary is indicative of a *separate group of proteins* The first boundary represents albumin the remaining boundaries globulins In order the latter are designated alpha 1 alpha 2 beta and gamma About 75 per cent of the serum lipids are carried in combination with the protein in the beta glob*ulin fraction Only a small proportion of* lipid is carried with the alpha protein fraction

How lipid and protein are combined and how tightly they are bound are not exactly known It has been suggested although not proved that there *is a core of protein with active groups* of amino acids on its surface This core holds these molecules together through attractive forces between non polar peptide residues such as leucine and phenylalanine and the fatty acid of the lipid moiety

What happens to lipoprotein in the blood stream in the utilization of lipids? It has been postulated that there is a normal level of lipoprotein in the blood That level is exceeded when lipoprotein is unable to take up more neutral fat that point is the high level of lipopro*tein fat combination Then from tissue* an enzyme or clearing factor lipoprotein lipase is released When it comes into contact with the lipoprotein it splits off the neutral fat fraction in glycerol and fatty acid thereby regenerating the protein to be available to pick up more lipids

In the biochemical approach to the study of genetic influence in any disease it is necessary to select a specific characteristic to be investigated In the present instance it may be a lipid constituent of the blood such as neutral fat Whatever it is its validity and significance is usually established through its occurrence in patients with clinical signs of a particular disease Also blocks and aberrations may occur in several ways *and in various stages in the metabolism* of a substance For one thing the metabolic block may be found to be a so

ciated with an enzymatic aberration Whatever the detectable abnormality the pecific characteristic is traced genet ically Sometimes the tracing is best undertaken in genetically i olated groups

Block pointed out that a metabolic abnormality may be found in either of two stages biochemically manifest or latent In some per ons it may be readily detected by an appropriate bio chemical method in others it is in a o called carrier state which may be revealed only after special measure For full and complete application of genetic principles detection of the carrier or susceptibility tate is highly important Perhaps one way to reveal this state is to impo e an appropriate stre or over load upon the subject Two examples illustrate the point When a family is being studied for occurrence of phenyl ketonuria the abnormality will be found regularly in the urine of some members but will not be detected in others However Jervi has indicated that the admini tration of phenylalanine to patients with this di order may lead to an abnormal phenylalanine tolerance curve Another means of detecting early evidences of di eases which develop late in life is a technic devi ed by Conn and Fajans which utilizes stres for the recognition of su ceptibility to diabetes In both examples the u cepti bility which would otherwi e go un noted is detected by a form of tre s Empha ized was the pos ible u efulne s of detection of the carrier tate in tudies of heart disease Practically de tection of the carrier tate open the po ibility of delaying or preventing the manife t di ea e

Block propo ed three tudies in a bio chemical genetic approach to heart di ea e In one the objective would be to mea ure the clearing ability of the era of per ons with hyperlipemia Normally the enzyme lipoprotein lipa e cannot be detected in the blood but if heparin i injected into the subject hi blood how within five minutes a rapid in crea e in its ability to clear neutral fat i e turbidity and hyperlipemia dis appear From these and other observa tions it ha been concluded that hepa rin produces a profound alteration in the lipoprotein pattern If this lipemia clearing test were applied to patients with hyperlipemia it might be po sible t detect whether they have a normal re pon e to heparin with liberation of the ti sue enzyme which i in trumental in the utilization of neutral fat or whether they have a di turbance in the relea e of the clearing enzyme

A a second study Block sugge ted that the level of lipoprotein fractions in the blood of per on in family groups hould be determined and the results genetically analyzed There i some evi dence to indicate that a carrier state may exist in hyperlipemic persons which is detected in the alpha lipoprotein frac tion From tudies on a large family through everal generations Adlersberg ha reported an aberration in the alpha lipoprotein

Third Block recommended that de tection of the carrier tate by biochemi cal method be applied to genetically isolated group It is here that the pro cedure has its greatest effectivenes As an example he described it application in the tudy of primary y temic amyloi dosi in a genetic i olate Upon ultra centrifugal analy is of erum lipoprotein from 66 subjects 29 how ed an ab normal pattern in the alpha 2 globulin region which corresponded approxi mately to the po ition of an atypical peak in electrophoretic diagrams Al though biochemical analy i of lipopro tein from individual with clinical igns wa important if only to e tabli h the clinical significance of the re ult it greatest u efulness wa in detecting the ubclinical the so-called carrier tate For the e rea on Block recommended tudies of the rel vant biochemical char

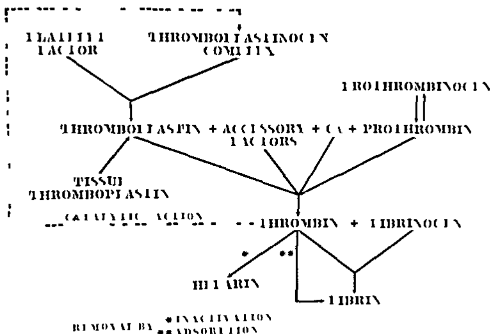


Figure 1—Schema of Blood Coagulation

acteristics of heart disease in genetically isolated groups

One of the most significant developments in the pathogenesis of coronary disease is the formation of a thrombus which may lead to occlusion. This possibility—an actuality all too frequently—raises several questions: whether the blood of some persons is in a hypercoagulable state, whether that state is measurable, whether it is attributable to an abnormality in the blood, and whether it has a genetic association. In approaching the subject Dr. Quick presented such evidence as is available. Then, as an aid to understanding both his explanation of his observations and the rationale of his subsequent opinions, he reviewed hemostasis, the process of blood coagulation, and the probable events in the formation of a thrombus.

In an attempt to determine whether a thromboplastic tendency could be demonstrated, Quick conducted a battery of tests on the patient with thrombophlebitis. These tests revealed no real abnormalities that would indicate a thromboplastic tendency. Unfortunately most available tests were not designed to detect coagulability but the opposite, hemorrhagic tendency. For example, in hemophilia the clotting abnormality can be attributed to the lack of a specific factor, thromboplastinogen (Factor VIII, antihemophilic globulin). But available methods useful in the study of bleeding tendency do not provide such reliable and complete information on hypercoagulability. Because of their limitations when applied to coagulability, the results yielded by these methods are open to question. In Quick's opinion hypercoagulability is measurable neither by the clotting time nor by any other test routinely used in the laboratory.

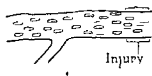
In view of the technical limitations Quick turned to a different approach. In raising and answering for himself the question what is hypercoagulability, he reasoned that essentially it must involve a greater amount or an increased rate of formation or reaction of throm

bin for after all it is thrombin that converts fibrinogen into fibrin in the formation of a clot Avoiding the more difficult and uncertain course of searching for ways to rai e the thrombin level by influencing factors that control its formation he went directly to the experimental production of a clot by injection of thrombin When thrombin in high concentration was injected rapidly intravascular clotting throughout the vascular system ensued But such large amounts of thrombin were necessary that obviously the experimental procedure was not comparable to the natural occurrence of any hypercoagulable tate Then too the clotting o far exceeded the extent which might be presumed to occur from a natural hyper coagulable tate that it did not repre ent an analog

I ut when thrombin was injected at a slow constant rate re ults oppo ite from what might be expected were obtained Instead of the clotting time being hortened it was prolonged One of the reasons for this seemingly paradoxical reaction is that thromboplastinogen drops to a very low concentration The level of Factor V is al o reduced What i actually produced i a hypocoagulable state which acts as a natural protector mechani m preventing the building up of a hypercoagulable state

F gure 2

HEMOSTASIS



1



2 Reflex contraction & retraction
a Nar owing of the lumen
b Decrease of blood flow



3 Gluing effect of injured endothelium



4 Platelet thrombus formation (clou hemostatique)
Liberation of a diffusible vaso constrictor principle from platelets



5 Fibrin clot
Continued liberation of vasoconstrictor principle

It hould le emphasized that it is thrombin which is the all important sub tance in coagulation There are two ways in which it is formed (Figure 1) In one it is produced in the blood per se i e blood completely i olated from tis ue This process requires a complex reaction a platelet factor and a pla ma factor the thromboplastinogen complex form thromboplastin this then reacts with prothrombin accessory factor and calcium to produce thrombin In a test tube it takes at least from five to eight minutes for that reaction to occur The slowness of the reaction rate makes it mo t unlikely that the body develops a hypercoagulable state by thi route

Quite different is the formation of thrombin from another ource tis ue thrombopla tin and by another route Ti ue thrombopla tin does not have to be manufactured during the clotting reaction It is widely di tributed in the tis ue When it comes into contact with other factors in the clotting sys tem there is rapid clotting in 12 econd It is ti ue thrombopla tin that could be the ource of hypercoag ulability

The first tep in arrest of bleeding i e hemo ta is is vascular con triction (Figure 2) It is a factor in intra vascular formation of a thrombus But the thrombus doe not form in the blood stream in tead it has its origin at the site of an injury to the vascular wall (Figure 3) This clot gets its tart from tissue thrombopla tin which leaks out the thrombus form rapidly be cau e of the quick action of ti ue thrombopla tin Then the thrombus can organize especially if the blood tream is fa t or the clot may attract platelet undergo contraction and extrude erum The erum contributes to further throm bosis with a new clot Provided it is not swept away by the circulation it is superimpo ed on the original throm bu A a result there may le ucces ive growth of new thrombi

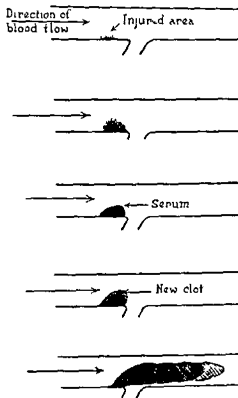


Figure 3—Probable Events in the Forma tio i of tl e Thrombo i

It is important to reiterate that the clot which is a sumed to play an im portant role in heart disea e does not originate from the blood it elf but from the vessel wall It is then coordi nated with the clotting factor Con sequently in Quick s opinion little knowledge concerning thrombo i is to le gained by study of the blood for coagulation changes Certainly the re ported re ult from studies on the in fluence of lipid on clotting are open to question Since the clot originates in the vessel wall it i there that the search hould be directed in studying coronary thrombo i

Heredity plays a more important role in hemorrhagic di ea e than in any other group of di orders Perhaps it may al o exert an influence over throm bo i But the chance are rather re

mote of finding blood changes indicative of a hypercoagulable state that may be relevant to coronary thrombosis and possibly attractive for genetic analysis. Focusing on the vessel wall seems more promising.

Dr Jarvik discussed the possible relationship of genetic influence to heart disease at various stages in the hypothesized sequence of its production. Conceivably there may be genetic relationships with both the general and specific aspects of the process.

From the studies of Wolff and Hinkle it has been concluded that when persons have illness associated with an adaptive reaction to disturbing situations they may develop any of a variety of diseases including cardiovascular disease. In a sense they may be regarded as being susceptible to many kinds of diseases. These persons may have a generalized constitutional weakness. From this conclusion it may be further inferred that all are capable of developing atherosclerosis provided that they live long enough and are exposed to appropriate environmental influence. In relationship to general constitutional weakness Dr Jarvik likened atherosclerosis to tuberculosis. With sufficient exposure everyone can contract tuberculosis. Yet there appears to be a genetically determined variation in resistance to this disease: some people succumbing more easily than others. The same relationship might hold for heart disease.

On the other hand genetics may be more specifically related to the production of heart disease. Not all persons do develop atherosclerosis. Many people die at 80 or 90 with no evidence of it. Only some persons have the capacity. Atherosclerosis can be developed only by those who have the potentiality presumably on a genetic basis. As in schizophrenia so in heart disease only those who have the proper genes contract it.

That both the constitutional and specific processes have a genetic relationship is possible, indeed probable. Conceivably all persons may have a potentiality for developing certain types of cardiovascular disease whereas only those persons with a specific combination of genes succumb to other types. Perhaps the psychological reaction pattern of certain people is based on a particular combination of genes which may be associated with a type of physiological activity that produces hypertension. It would be important to determine these points because at present there is no genetic evidence for them.

To stress, genetic influence may be related in two ways: (1) Genetic effects may be largely responsible for the situation creating stress; (2) genetic influence may affect the individual sensitivity and reaction to stress. Situations creating stress may exist in certain families because genetic factors have contributed to the production of other diseases. In families with mentally defective members or schizophrenics the group is exposed to a greater degree of stress than is usual. It would be informative to determine the incidence of heart disease in families experiencing this additional stress. A study is now being conducted to find out whether the stress created by such a disabling condition as deafness, which is in part genetically determined, increases the incidence of schizophrenia in the family.

In the search to ascertain whether the various pathological changes in heart disease have a genetic relationship, the avoidance of one particular pitfall should be emphasized. Any disorder that is genetically determined has its counterpart on an environmental basis. The environmentally produced disorder which is called a phenocopy mimics the genetically determined form so closely that the manifestations of the two types are indistinguishable.

Methodology.—In order to answer questions concerning the bearing of

genetic influences on heart disease both twin and family studies are needed One of the most important objectives should be to ascertain whether genetics exerts an influence on cardiovascular disease and if so whether it would be possible to identify individuals who are particularly vulnerable to the disorder Then it would be useful to apply studies of twins in a somewhat different way than is usually done Once vulnerable individuals can be identified it would be profitable to search in the environment for significant variables that affect them and bring them down with cardiovascular disease Because it would be reasonably certain that such a group has the potentiality of developing the disease it would be the only group in which the influences of environmental factors could be so readily studied

Originally twin studies were designed to reveal the importance of genetic factors by comparing the rates of prevalence of a disease in twins and siblings Just as valuable if not more so would be twin studies in conjunction with experimental exploration of environmental factors When used in conjunction with the application of therapeutic methods twin studies could be very useful in investigating physiological and biochemical variables

In exploring the environment for relevant and significant variables it is helpful to follow clues By the same token it is more important to ask the right question than to test a random series of correlations Studies already under way have indicated a greater correspondence of levels of blood constituents between identical twins than between siblings On the basis of these observations it is suggested that when the individuals who are most vulnerable to cardiovascular disease have been identified it be ascertained whether levels of blood pressure and lipoprotein in the blood are at least in part genetically determined

A genetic evaluation should be a part of any epidemiological study A number of simple test factors exist that enable the investigators to detect gross genetic differences within the group or groups being studied

The application of genetic technics to cardiovascular disease may be divided into three broad areas

1 Gathering of Information — Complete family history (including infant deaths) an objective description of the subjects physical characteristics identification of the subjects with their known relatives presence or absence of consanguinity history of exposure to radiation In countries where registries exist these should be utilized

2 Mass Screening Laboratory Technics — Electrophoretic analysis blood typing specific antigen antibody reactions chromotography urinary amino acid excretion patterns (urinary tests for alcoptonuria cystinuria galactosuria and pentosuria) enzyme determinations cytological and sex determination Particularly useful in terms of mass surveys would be the application of carefully designed overload tests to detect the latent state or the carrier state of certain metabolic abnormalities

3 Studies of special groups such as genetic isolates and twin family aggregates

Lilienfeld has recently published results on a methodological problem in the study of familial aggregation of disease In particular he investigated the application of a binomial test to determine the consistency of observations with a recessive gene hypothesis His results indicated that this method had a low ability to discriminate between genetic and nongenetic hypotheses In accord with the published opinions of several geneticists he drew attention to the difficulties and pitfalls in determining whether a disease is inherited

EPIDEMIOLOGIC METHODS IN CURRENT CARDIOVASCULAR DISEASE RESEARCH

Ralph S. Paffenbarger, Jr., M.D., F.A.P.H.A.; and D. E. Krueger

During the six-month period ending in March, 1959, we have had opportunity to review a series of epidemiologic studies of cardiovascular diseases currently under way across the nation. Twenty-one of these studies deal with some aspect of hypertension or arteriosclerotic heart disease, and thus their study methods may be of interest to the members of this conference. An over-all view of these study methods is given as well as brief descriptions of each of the 21 studies. Abstracts of eight, which perhaps have been less widely discussed than the well known endeavors at Framingham, Albany, etc., exemplify the range of methods employed and are incorporated in the body of this report. Abstracts of the remaining 13 are included as an addendum.

Study Methods

The application of epidemiologic methods to the study of arteriosclerotic heart disease (ASHD) and hypertensive heart disease (HHD) is taking three approaches: descriptive, analytical, and experimental. (1) In the descriptive approach observations on recognized diseases are made in terms of chronologic and geographic distributions and the characteristics of patients. Personal attributes of patients are contrasted with similar attributes determined from census figures or some other available source for residents in the patients' community. (2) In the analytical approach independent variables are identified and related to the occurrence of disease. The frequency of specific host or environmental factors and the frequency of disease are each determined. Population being studied are divided into those with and those without disease and in each group the proportion with common personal attributes is ascertained. Also the proportions of diseased and of nondiseased populations that engage in a common practice, encounter similar incidents, or are exposed to similar potential risks are measured. (3) In the experimental approach human volunteers are induced to change their habits or environmental factors are altered and the effect of these changes on disease is measured.

Regardless of the approach used, the purpose is to determine whether individuals characterized in one way, such as by a physiological or socioenvironmental factor, are differentiated in a second way, as by a disease. For example, one might determine whether a difference in the frequency of coronary heart disease (CHD) exists between a group with premature presbyopia and another group without it. The essence of the approach is comparison, and it is encouraging that investigators are greatly concerned with standardizing their observations and accurately classifying persons by the presence or absence of two variables, the factor in question and the disease, in order to make valid comparison possible. The scientific requirement of assessing the socioenvironmental variable independent of the clinico-laboratory variable is being met. For the most part attention is given to other influencing variables through selection

of study subjects or through adjustment by accepted statistical technics. Uncertainties in diagnosis of disease lead to use of probable or borderline classifications and most socioenvironmental factors are measured on a gradient scale. Thus comparison of the disease variable and the socioenvironmental variable usually is not limited to a two by two correlation.

The search for association between either ASHD or HHD and any of a number of host or environmental factors uses one of three methods. First, contemporary studies of diseased and disease free persons are providing snapshots or prevalence figures of the specific factors under study. Second, studies that are longitudinal in time are picturing flashbacks to an earlier period by measuring (through interview, past medical record, and similar data) the proportions in the disease group and in the disease free group that have experienced the same specific factor. Last, longitudinal studies are following individuals through a period of time in motion picture fashion and by means of appropriate clinico laboratory tests are making initial and successive determinations of the frequencies and magnitudes of the diseases and the factors.

Populations being studied include (a) hospital or clinic patients, (b) closed populations in institutions, and (c) groups of persons in communities at large. These populations ordinarily are chosen to meet a specific requirement of the study design.

The abstracts of study methods reviewed here are necessarily brief. Responsibility for omissions, inconsistencies, or inaccuracies in these abstracts is ours and not that of the investigators who supplied the information.

Current Studies

1. Navajo on Reservation—The first study to be described is being conducted out of the Western Navajo Hospital in Tuba City, Ariz. The frequencies and distribution of cardiovascular diseases (CVD), particularly coronary heart disease (CHD), among the Navajo are being observed. Specific aims are to determine (a) the prevalence and incidence of CHD, (b) the serum lipid patterns of adult Navajo males, (c) the make-up of the Navajo dietary, and (d) the geographic and demographic characteristics of Navajo subgroups on the reservation. These endeavors were prompted by prevailing clinical impressions and published reports to the effect that the Navajo experience less CHD than the white or Negro races. The design of methods includes the examination of 150 adult Navajo males who were considered healthy and without clinical or laboratory evidence of diabetes, renal disease, or thyroid disease. Clinico laboratory examinations of snapshot type are being performed and for comparative purposes similar measurements are being made on a selected series of healthy white males seeking routine medical checkups in a medical clinic in Albuquerque. In addition, the heart and aortas of Navajo and clinic patients coming to necropsy are being examined for atherosclerosis. (Approximately 50 per cent of the Indians who die in the Fort Defiance Navajo Medical Center or in the Western Navajo Hospital come to necropsy.)

2. An example of the motion picture method applied to an open population is the study in Evans County, Ga. The study has been activated in search of precursive factors of atherosclerosis and its sequelae. The total county census (by age, sex, race, address, and place of birth) has been determined from vital records, list of utility subscribers, newspaper solicitations, and house-to-house canvasses. The census is being kept current by periodic recheck using these same counting devices. Morbidity

and mortality data are obtained through physician vital records and hospital data. The county with a population of 7,500 and a two to one white to Negro distribution is largely rural and is served by two practicing physicians. One of the physicians is the sponsor and principal investigator in this study and the other cooperates closely. Marked rapport exists among the physicians and their patients who comprise essentially the total county population. Necropsies are requested on the death of each county resident and are performed by a consulting pathologist on approximately 50 per cent of decedents.

Relative rates of CHD by race and sex groups are being determined longitudinally from (a) physician, hospital, autopsy and vital records and (b) successive censuses of Evans County. This phase of study will continue through calendar year 1960.

Blood specimens for serum lipid determinations are being drawn from approximately 1,200 adults listed on the Evans County census registry. Subjects are chosen through use of a stratified sampling technic. Laboratory testing of specimens permits comparison of lipid levels by age, race, sex and season of the year in which the samples were collected.

For one physician's office practice all patients aged 35 years and over who seek medical advice or treatment for any illness are being followed over a five-year period (mid-1958 through mid-1963) for the occurrence of CHD. To the degree that a busy practice permits, the following data are being recorded on each patient at least once annually: (a) family and personal history of heart disease, (b) results of a general physical examination and (c) findings from serum cholesterol and alpha and beta lipoprotein tests. When patients do not return within a year they will be contacted and lipid determination repeated as a minimum examination. All overt attacks of CHD and deaths from this cause will be recorded as they are recognized. Biennially the health status of each participant will be reviewed through telephone or personal contact. Through records of such repetitive observations and laboratory determinations it is expected that some of the precursors of CHD may come to light.

The influence of sex, race and stress factors (physical and psychological) on serum lipid levels of children from birth through preschool ages is being determined. Umbilical cord blood samples are being collected at most deliveries in the county and repeat blood samples are drawn at six-month intervals. These specimens are being tested for levels of cholesterol, alpha and beta lipoproteins, and the lipid mobilizing factor. The race, sex and birth weight of each infant are recorded together with weight and illness histories at each six-month interval.

Studies of school-aged cohorts are patterned after the newborn studies with effort being made to enlist all school children in the county. More than 95 per cent have received parental approval to participate and are being entered in the study as rapidly as laboratory facilities permit. Repeat blood samples are being drawn at annual intervals and special interest centers on the influence of puberty on serum lipid level.

3. The snapshot method is being used at Louisiana State University School of Medicine in study of atherosclerosis. Procedures have been standardized for staining arteries with Sudan IV and for preserving them in flat, transparent, durable plastic bags. Also a method of grading human aortas by which different pathologists secure similar results has been developed and used to estimate macroscopically the extent of fatty streaks, fibrous plaques and complicating lesions (hemorrhage, ulceration,

thrombosis and calcification) Current studies seek information on pathogenic mechanisms through description of aortas and other arteries from necropsies on individuals aged one year and over Specimens are received from general hospitals and medico legal services in New Orleans Guatemala Puerto Rico and Colombia Special attempts are made in these geographic areas to necropsy all deaths regardless of cause All aortas most coronary arteries and more recently cerebral arteries are graded as to intimal lesions Physical studies (photographic light refraction and colorimetric) and chemical studies (quantitative and qualitative determinations of lipid) are in progress on a sample of specimens to (a) develop a grading scheme that does not require personal judgment and (b) search for age sex and racial differences in pathologic lesions An endocrine project including urine assays is being developed to permit correlation studies with atherosclerotic lesions

As a second study observations on zoo reared baboons have suggested that this widely prevalent ape which is first order below the anthropoid might lend itself as an ideal experimental animal for atherogenic studies Hence an African expedition was undertaken in the summer of 1958 to obtain baboons from their native habitat A total of 163 animals was captured and sacrificed for pathologic examination Specimens permitting estimation of chronological age and degree of atherosclerosis were shipped to New Orleans for study (Age estimates are being made from skull teeth and bone specimens together with measurements of body weight and size)

4 Out of the Georgia State Health Department a motion picture study of two circumscribed populations is in progress Since October 1957 serial observations have been made on residents of two monasteries in study of dietary regimens as they may relate to arteriosclerotic heart disease (ASHD) One monastery quarters members of the Trappist order whose religious dictates require a meat free lactovegetarian diet The second monastic population comprises Benedictine monks who are omnivorous and consume a diet essentially comparable to that of citizens at large in the United States Quantitative and qualitative dietary records are collected on selected fast feast and regular days in order to compute average intakes per monk per day Yearly clinico laboratory examinations and medical records during any period of hospitalization permit evaluations of illnesses including ASHD Blood specimens drawn quarterly are subjected to a battery of tests for lipid and protein determinations Participation in this ongoing study is voluntary with more than 95 per cent of the Trappist community and a comparable percentage of residence stable Benedictines enrolled

Eighty two Trappists ranging in age from 20 to 80 years (median age=35 years) are participating These monks live rigorous lives in primitive physical setting without modern conveniences Their work is largely of heavy manual types which is interspersed with sedentary hours for meditation There is essentially no verbal communication among the monks On days selected for determination of diet intake each monk keeps a record of his consumption by noting during meals the amounts and types of food ingested Uniform servings and the use of standard spoon sizes facilitate accurate reporting Tobacco and alcohol are not used by these monks

Sixty five Benedictine monks of an older age range (median age=40 years) than their Trappist peers are participating They live in modern dormitory type structures engage in relatively less physical exercise and are largely a teaching order Their diet permits little freedom of choice qualitatively but

contrary to that of the Trappi t allows for more quantitative election A food model demonstration is presented at the monastery to a si t the monk in making quantitative e timates of their intake A small proportion of members of this order u es tobacco an l a ome what larger proportion uses alcohol

5 A combination of snap hot fla h back, and progres ive motion picture methods i in u e at Beth El Ho pital Brooklyn N Y In progress over the pa t two years this study is de igned to determine whether pecific somato types are as ociated with a coronary diathesis and if so for what rea on Members of a fraternal organization are invited to a cancer and heart di ease detection clinic for specific clinico lab oratory te ts that permit classification by body type coronary heart di ea e tatus socioeconomic stratum and cholester olemia and estrogenuria levels The base population from which subjects volun teer to participate consi ts of 35 000 residence stable Brooklyn males who carry health insurance Participants are somewhat health con cious adults who largely lead a sedentary life and eat high fat diets Sixty per cent are salesmen and 95 per cent are married They are queried as to dietary and social habits and cla sified into types of body build by the ame examiner A econd examiner evaluates their car diac status through admini tration of a medical history physical examination and electrocardiogram (ECG) tracing Their attack rates of CHD are being as essed through (a) annual reexamina tions and (b) reports on cardiac mor bidity and mortality from their health insurance plan which includes phy i cian and hospital coverage One hun dred elected subjects in each of the three basic omatotypes (ectomorph mesomorphs and endomorphs) are being examined for estrogen level by analysis of 24 hour urine amples

As an independent tudy the degree of coronary atherosclero is and the type of body build are being a essed for all individuals dying suddenly and coming to medical examiner s autopsy in We t che ter County N Y The collection represents a 10 year experience and compri es largely deaths from automo bile accident

6 Sometimes referred to a a human population laboratory studies in prog ress at the Univer ity of Michigan School of Public Health maintain a current inventory of people place and things Over an 18 month period nearly all residents of Tecumseh, Mich and adjacent residential area have been characterized by demographic and other factor The prevalence of 11 chronic di ease conditions has been de termined for this group through elf administered questionnaire form The total population of approximately 8 300 person has been identified by hou e hold (N=2 400) familial and kindred (N=3 400) aggregation An additional 1 000 persons from neighboring com munities who are relevant to the blood line aggregates have been identified

Through even con ecutive monthly reports received by mail from each household new occurrences of illnes have been determined Al o tudy ha been made of the phy ical facilities and of the receptiveness of lay and medical groups to future more inten sive studies in this population The collected data have been analyzed a a lead eeking device and to determine the suitability of the population for ub equent epidemiologic tudy of a variety of chronic di ea e entities On the ba is of these analy es the inves tigators are satisfied that the commu nity lends itself to productive future tudy ince (a) the ingle large indus try in Tecum eh is relatively table and the population i nonmigrating (b) adequate numbers of individual over the entire age pectrum are avail able (c) a high prevalence of numer

ous chronic diseases exists, and (d) new cases of CVD occur with a frequency which permits testing of many hypotheses over a several-year period.

Early identification of individuals as to their susceptible or immune status in reference to heart diseases through both snapshot and motion picture studies is under way. (Other chronic diseases will be studied in similar fashion.) Specific aims include (a) identification of individuals with heart disease and associated condition; (b) search for associations between factors of host, environment and specific types of heart disease; (c) analysis of data by kindreds in search of familial influences and genetic patterns; (d) description of the frequencies and distribution of cerebrovascular accidents (CVA) and determination of their relationship to heart disease; (e) examination of heart disease patterns for relationships among congenital, rheumatic, arteriosclerotic and hypertensive heart disease; and (f) initiation of similar studies of chronic disease other than heart disease. Procedures entail the examination of Tecumseh inhabitants, residents of surrounding area, and kindred in neighboring communities (N = approximately 9,500). Methods include taking detailed medical histories by trained lay interviewers, review of these histories by physicians who perform physical examination and laboratory examinations.

As another study, blood pressure levels among Bahama Negroes have been measured to determine prevalence ratios of hypertension and to compare the findings with similar data available for Negroes living in the United States. One study is based on the clinical record of the single physician on the Grand Bahama Island and pertains to approximately 60 per cent of the inhabitants.

A third study relates to blood pressure determinations made by an epidemiologist and medical students from the University of Michigan on 3,000 individuals chosen as a probability sample of Nassau City on Providence Island. Demographic, social and cultural data have been collected on these subjects, a large proportion of whom are Negroes. Drinking water samples from selected communities have been collected for sodium determinations since the water frequently is brackish, and association between water of high sodium content and hypertension will be looked for.

7. At the Johns Hopkins University School of Medicine and School of Hygiene and Public Health two different methods of study and two different types of population are being used in search of factors associated with CVD. Since 1916 medical students at the Johns Hopkins University have been used as subjects in a study designed to identify those characteristics which may be of value in predicting and in preventing an early onset of CVD. To date nearly 1,000 students have been classified by a variety of genetic, physiological, psychological and metabolic characteristics in search of those traits which are associated with CHD or HHD. The CVD heritage of each student is assessed through family histories taken on parents, grandparents, uncles and aunts by the students themselves in their third and fourth years at Hopkins. On the fifth and tenth anniversaries of graduation each student is reevaluated by mail questionnaires concerning his health status and sociophysical habits. The health status of his parents also is redetermined. Under the assumption that students experience greater risk of developing CVD if they have an unfavorable CVD heritage, constitutional differences between low and high risk student groups have been identified. Based on observations to date, a four-way grouping of healthy students according to parental history and student characteristics has been proposed as a basis for selecting highly

susceptible individual. The individual positive traits in this grouping include (a) higher serum cholesterol levels, (b) nonectomorphic body build, (c) higher blood pressure level, (d) tachycardia, and (e) blood pressure hyperreactivity to cold or exercise. A student with two or more such positive traits is classified as having positive individual characteristics. The parental positive traits signify that one or both parents had a history of coronary or hypertensive disease. Follow-up data on health will be related to these characteristics.

As an independent study the death certificates of Baltimore residents aged 45 years and less who died between 1951 and 1959 have been categorized by cause of death in search of factors predisposing to ASHD. Subjects with death ascribed to ASHD have been subclassified into one of three categories following validation of death certification through review of hospital, physician, and autopsy records. These categories are (1) definite ASHD, (2) uncertain ASHD, and (3) definitely not ASHD. In the period under study death certificates with diagnoses of ASHD included nearly 200 subjects with a validated diagnosis of ASHD (Group 1), 250 with uncertain ASHD (Group 2), and approximately 100 with diseases other than ASHD (Group 3). All other Baltimore decedents in this age class (45 years and less), except those dying of accidental causes, are classified into a fourth category (Group 4). Individuals whose death was ascribed to ASHD (Groups 1, 2, and 3) are then matched by age, sex, race, and date of death on a one-to-one basis with individuals classified as having died from other than ASHD (Group 4). Survivors (spouses or siblings) of the deceased are interviewed by nurses making home surveys for specific and detailed information on family history of ASHD, alcohol and smoking, other disease, marriage and reproduction, and psychic and physical stress. Through cross-correlation analyses those factors of host which are associated with early death from ASHD are being sought. In search of precursors of ASHD, serum cholesterol and serum uric acid determinations are being made on a sample of the decedents' children and spouses in each of the four groups.

8. Two studies are being conducted by workers affiliated with the Health Insurance Plan of Greater New York and Columbia University College of Physicians and Surgeons. The first is aimed at determining the influence of female gonadal function on the development of CHD. The method employs the measurement and comparison of CHD prevalence in oophorectomized and in a control group of non-oophorectomized hysterectomized women. White female gynecological ward patients aged 45-65 years from the Columbia Presbyterian and Mt. Sinai Hospitals are being included in the study. Other hospitals will be added if necessary to realize the population of 700 oophorectomized and 1,300 non-oophorectomized subjects estimated to be needed in order to determine whether there is a difference in CHD prevalence. Test and control groups are being matched by (a) period of operation within three-year grouping, (b) age at operation, and (c) nationality or country of origin. Patients with hypertension or diabetes at time of operation are eliminated from the study. Study subjects are identified through medical record review and then contacted through one or another of the following methods: (a) telephone, (b) attending gynecologist, (c) social service exchange, (d) return United States mail (Form 3547), (e) Welfare Department, or (f) visits by a retail credit agency. When notified of a death the investigator obtains a copy of the death certificate. Survivors are invited to the hospital for medical

and laboratory examinations A history of e trogen administration is obtained from the patient s family physician The criteria for diagnosis of CHD rest largely on history of episodes and current ECG tracings The study will continue until interpretable results are obtained

The second study is that of CHD survivor hip and repeat attacks It has been activated only as a pilot undertaking thus far utilizing new cases reported from three HIP Medical Groups Patients are invited for examination by a single physician and for appropriate laboratory examinations Serial medical checks are planned at six month intervals for two years and biennially thereafter Attention will be given to clinical manifestations that develop as well as to mortality

Discussion

In general the studies reviewed here employ methods which have been developed and extensively applied in the study of infectious di eases The process is that of measuring and comparing the frequencies and di tributions of disease within defined populations The aim is to identify or unmask those factors and conditions that cause disease In regard to causation it is recognized that the inability to ee the dynamic pro esses of pathogenesis in human subjects calls for use of the *epidemiologic* method and the inductive reasoning on which it depends

Of the three methods being used in earch of associations between cardiovascular di ea e and host or environmental factors—termed snapshot flashback and motion picture for convenience of description—it is generally agreed that motion picture studies provide the most comprehensive and accurate data The three study types are complementary however and are most effective when they are u ed in combination

The investigators interviewed are aware that the mere demonstration of statistical a sociation between a given factor and a given disease does not establish the link of causation between the two events Rather such an association simply indicates that a change in the frequency or magnitude of one event is accompanied by a change in the frequency or magnitude of the other A given event shown to be directly associated with a given di ea e may repre ent only an index of a second event which is in fact a true cause

Procedures to distinguish temporal association from causal relation hip must be designed to fit specific situations and conditions Such differentiation requires a thorough knowledge of biologic concepts of the disea e together with the conduct of studies that would test specific hypotheses Procedures would seek to verify by further facts to establish ancillary evidence to reproduce results under different circumstances or to develop alternative hypothe es

Uncertainty exi ts as to whether the factors presumed to be related to CVD represent primary or econdary etiologies—that is are they definitive cause or in contrast do they provoke clinical attack in individuals harboring a primary cause? Do such factors as hypercholesterolemia hypertension obesity and the *like compri e definitive* or only predi posing etiologies of CHD? These questions thus far unanswered may prove analogous to the interactions between primary and secondary etiologies in acute poliomyelitis In this disease three immunologically distinct viruses comprise e sential cau es and such factors as pregnancy oropharyngeal surgery and the intramuscular inoculation of antigens have been e tablished as contributing causes

Current and Proposed Study Factors

The 21 studies which we have reviewed are measuring a variety of environmental and physiological characteristics in addition to those on which information is obtained in the course of a routine diagnostic examination—medical history, social history, physical examination, and laboratory tests. Table 1 shows a partial list of these additional factors, the number of investigators currently measuring each factor, and the number of other investigators among the 21 principal investigators who were proposing but had not yet begun to measure the respective factors at the time of our review in early 1959.

Decision to measure a particular factor implies that some hypothesis about that factor and the occurrence of disease is being tested. For any given factor different measurements are being made from study to study.

Diet is the factor of interest to the largest number of investigators: ten are currently measuring diet and seven others propose to do so. Four are now using some measure of psychic stress and five others plan to measure it.

The items physical stress and occupation require some explanation. Physical stress refers to the administration of some test of reaction to exertion such as an ECG after exercise, whereas occupation refers to a job classification as an index of physical activity.

Environment change as used here means an attempt to alter a specific characteristic, e.g., dietary intake, and to measure the effect of this change on the occurrence of disease. A decision to undertake environmental change rests not only on confidence that an association exists between an environmental characteristic and occurrence of disease but also on the idea that a change in the environment will be accompanied by a change in the occurrence of disease. The problems of measurement of the factor still exist and may be made more difficult because of the fact that the investigator has induced an ecologic change.

It is apparent from this list of factors being measured in current and proposed research that the subject areas of measurement selected for attention in this Conference on Methodology are of immediate and major importance in epidemiologic studies of CVD.

Table 1—Environmental and Physiological Factors Measured in 21 Selected *Population Studies*

Factors Measured	Population Studies *Current*	*Proposed*
Psychic stress	4	5
Physical stress	3	2
Dietary	10	7
Occupation	8	0
Environment change	1	2
Lung function	3	0
Skin fold	5	0
Clothing	2	2
Endocrine	5	1

Summary

The methodologies being employed in a series of epidemiologic studies have been reviewed. By means of measurement and comparison the aims of these studies are to determine whether persons manifesting specific physiological or socioenvironmental factors experience a different risk of cardiovascular disease than do persons without such factors. Associations are sought between a specific disease and a specific factor through (a) contemporary studies providing a snapshot of the two events, (*b*) *chronological studies picturing* flashbacks to an earlier period, and (c) long-term studies of progressive motion picture type. Groups under study include closed or open populations that are chosen at random or selected on the basis of some preexisting condition.

It is recognized that the success of both current and proposed epidemiologic studies will rest on standardized observations and on precise classifications of persons according to the presence or absence of two variables a specific factor and a specific disease Follow up studies will attempt to distinguish between associations that are only statistical and those that reflect a causative relationship To this end epidemiologic studies will complement clinico laboratory efforts by providing collateral evidence by verifying amplifying or modifying prevailing concepts or by developing alternative hypotheses It is anticipated that application of epidemiologic methods to the study of chronic diseases will lead to evidence consistent with a causative hypothesis as have such methods in the study of acute diseases

Addendum

9 Framingham Mass —This longitudinal study began during the period of 1948 to 1950 and has run continuously to date Serial observations have been made on over 4 000 individuals or 69 per cent of an initial randomly chosen sample that represented two third of the Framingham population aged 30 to 62 year Biennial medical histories physical examinations and laboratory tests have provided the data for study Reports from local practicing physicians and hospitals have complemented these record The study s initial aims were to obtain descriptive information on CVD and to measure prevalence and incidence of these diseases in the population Secondary purposes were to test selected hypotheses concerning causation of heart disease these hypotheses being constructed from clinical impression or the epidemiologic findings of others To date major effort has been directed to ASHD and HHD and to associations between these diseases and specific factors of host Foremost among these factors have been hypercholesterolemia hypertension and obesity More recently other factors have been added and include dietary habit alcohol consumption tobacco usage educational levels lipoprotein measurements and district of residence in Framingham Plans call for extension of the study over at least ten more years

10 Connecticut State Health Department—Studies began early in 1957 with the initial aims of (a) measuring the prevalence and incidence of CHD and CVA in Middlesex County and (b) testing specific hypotheses concerning causation of myocardial infarction (MI) as related to particular dietary habits and to social and personality correlates of stress Case finding has been achieved through report from practicing physicians and hospital coupled with death certifications A 10 per cent probability sample of the population was queried through Bureau of Census interviews to provide population estimates for rate denominators an independent estimate of clinically manifest CHD and control series for the comparison on phases of the study i e the nutritional and sociopsychological phases

The sociopsychological aspects of the study contrasted a sample of white male patients aged 55 64 year who survived an attack of MI with an equal number of patients suffering from an acute severe illness other than heart disease and matched with the test group by (a) age to within five year (b) race and sex (c) occupational level and (d) ethnic origin traditionally similar to that of the test subject These studies continue and are currently directed at refinement of both hypotheses and tools of measurement

11 New York State Department of Health—A long term project began in 1953 a repetitive observations on nearly 2 000 male Civil Service employee aged 39 55 year from the Albany

area Participants represented 89 per cent of the population invited into the study Primary objectives have been (a) to evaluate established methods of early detection of all forms of heart disease (b) to evaluate new technics for this purpose and (c) to look for etiologic factors of CHD Annual physical examinations and medical histories by physicians as well as self administered questionnaires have provided the data for study Clinico laboratory measurements have permitted a wide search for factors associated with all types of CVD Special emphasis has been placed on the study of potential nutritional influences on these diseases The study proceeds in standardized fashion with more intensive clinical observations being made on subsamples of the study population

A second project began in early 1955 and continues to date It comprises a study of consecutive autopsies from a general hospital and the comparison of cardiac pathology with ante mortem characteristics and environmental exposures of the decedents The principal purpose is to search for etiologic factors of coronary occlusion and MI Observations at necropsy include measurements of the lumens and thicknesses of coronary vessels Observations concerning the autopsied subjects are made through medical student interviews with a close relative of the decedent Other social and environmental details are obtained from the usual family physician and life insurance medical records of the deceased Selected characteristics being studied include nutritional factors usual occupation weight alcohol consumption tobacco usage and so forth Comparisons on these characteristics are made between individuals dying of heart disease and individuals dying of other diseases It is expected that the study will be extended beyond the current population of approximately 900 autopsies

A third study is being started which contrasts by retrospective means cases of MI with matched control subjects The case population is being obtained by a carefully developed and vigorously monitored reporting system from all physicians in Albany County Reporting includes cases with other manifestations of CHD but detailed study is being limited to survivors of first infarctions Control subjects matched on five characteristics (age sex race socioeconomic status and urban rural residence) are drawn from a 5 per cent census of the population It is estimated that 500 cases matched with an equal number of controls will be collected by 1961 Comparison of these populations will be directed primarily toward the variables of diet physical activity and chronic emotional stress although a number of other characteristics are being studied

12 Columbia University College of Physicians and Surgeons Harvard Medical School and University of British Columbia Medical School—For the past 12 years a group of 100 sympathectomized (Smithwick operation) hypertensives and an equal number of untreated hypertensives have been followed to assess the effect of this operation on survival Pairs of test and control subjects were selected from hypertensive clinics in New York City Boston and Vancouver They were matched by (a) age race and sex (b) average and range of blood pressure readings (c) cerebral symptoms and complications (d) cardiac size and ECG pattern (e) histories of angina or cardiac failure and (f) other factors including degrees of proteinuria eye ground changes and renal damage Each of three investigators reviewed clinical and survival data on all pairs in a blind fashion at two five and ten years after subjects were entered into the study

Independent studies of similar

matched control type are being undertaken at Columbia using groups consisting of 25 patients each to test specific hypotheses These groups will provide information on relative survival rates of (a) patients with malignant and essential hypertension and (b) drug treated and untreated hypertensives

13 New York City Health Department—This project began in February 1957 to determine (a) if it were feasible to achieve dietary control in a free living population and (b) if such dietary management would reduce total cholesterolemia and lower coronary heart morbidity and mortality Male volunteers willing to follow tailor made dietary patterns were solicited through two newspaper announcements They were included in the study after attending an orientation lecture if they expressed willingness to follow a prescribed (prudent) diet over many years perhaps until age 65 years Originally the study included males aged 50 59 years but this has since been broadened to include age classes from 20 through 59 years

When a subject enters the study a medico laboratory examination is conducted and a comprehensive diet history covering the two preceding weeks is obtained by personal interview with the subject and his wife The interview permits an estimate of all nutrients as well as the intake of total calories and calories from fat If the subject is judged by clinical means to be overweight he is put on a weight reducing diet When a normal weight is achieved the subject is placed on a prudent diet that includes a fat intake providing about 30 per cent of total calories Fats are divided half and half into saturated and unsaturated types of fat (Part of the latter is given in such forms as specially prepared margarine containing 80 per cent unaltered corn oil and a milk constructed from a homogenized mixture of fat free powdered milk vegetable fat and water)

Serum cholesterol levels are measured at weekly intervals at the outset to establish a base line which is computed as an average of two or more determinations within 10 per cent of the lowest Follow through is attained by (a) annual medical examinations with ECG tracings (b) serum cholesterol measurements and diet and weight checks every four weeks and (c) sessions with a board of review (physicians) every ten weeks to discuss the individual progress Subjects provide medical data at the ten week check and hospital information where it exists complement this Subjects are told that they will be followed personally until age 65 years and thereafter through Social Security records

14 University of Pittsburgh Graduate School of Public Health—The mortality experience in (1) the Arsenal Health District of Pittsburgh during the interval 1951 1956 and (2) Donora Pa from 1948 to 1957 has been reviewed Mortality has been examined in relationship to prior findings of morbidity surveys in each area (The Donora survey of 1948 investigated the health effects of smog exposures in October of that year The Arsenal survey was undertaken to measure the frequency of chronic illnesses and medical care in 1951) Together with these mortality studies the surveys of these populations have permitted prevalence estimates of various chronic conditions including heart diseases Findings have convinced the workers of a need for (a) more detailed observations on recognized cases of all diseases and (b) a better understanding of the timing of onset of overt heart disease and its progression Forthcoming studies in a group of industrial employees will give attention to these problems

15 Presbyterian St Luke's Hospital

—A five year tudy of heart di eases among a large group of industrial em ployees began in the fall of 1957 with particul ir emphasis on CHD Study ubjects were men aged 40 55 years who had been employed two years or more in a Chicago electronic indu try and who on review of the company medical record were believed not to have had either MI or angina pectoris when the study started A total of over 3 000 men was randomly cho n from the complete ro ter of company em ployees and invited to participate Over 2 100 (70 per cent) complied have been examined and are now in the econd round of examinations The aims are (1) to determine the cardiovascular status of ubjects at the time of the initial examination (2) to measure in cidence of heart disease through four annual reexaminations and (3) to re late the incidence of heart di ease to various physiological measurements and other characteristics of the subject Data gathered at the initial examina tion included (a) a family hi tory pre pared by the subject (b) a medical hi tory and physical examination by one of 25 volunter physicians as isting in the tudy (c) clinico laboratory te ts including somato typing with photog raphy (d) diet a sessment by detailed interview with the subject and a ques tionnaire completed by the spouse (e) phy ical activity measurement by analy is of job requirements and an inter view concerning off the job phy ical ex ertion and (f) personality traits deter mination as revealed by the Minne ota Multipha ic Personality Inventory These procedure are being conducted in facilitie at the plant and require about two half days for which the ub ject is given time off with pay

16 Tulane University—Since 1951 the influence of hot and humid (ub tropical) environments on phy iologic and pathologic respon es in man ha been under tudy Observation are being made both in hospital wards and in experimental chambers using normal ubject and patients with chronic con ge tive heart di ea e Mea urements of cardiac function are being contra ted between study population and temporal compari on are being made within the e populations

17 South Carolina College of Medi cine—Clinico laboratory procedures have been developed and standardized to per mit screening of large numbers of ub jects for (a) blood lipid levels (b) whole blood coagulation and (c) in travascular agglutination of erythrocytes (ludging) Interrelation hips among the e variables are being sought for everal contra ting groups including (a) elected di eased and normal popula tion and (b) samples of white and Negro residents of metropolitan Charles ton A battery of lipid tests are being run on all blood erums including those for cholesterol pho pholipid tri glyceride and alpha and beta lipopro teins Microscopic ob ervations photo graphs and closed circuit televising of the capillary circulation in the bulbar conjunctiva allow estimation of the de gree of erythrocyte agglutination and arteriolar plugging with ludged ma e Blood coagulation is measured by con ventional technic

18 California State Department of Health—In 1948 a total of 577 healthy individual aged 50 years or more were selected from 843 regi trants who vol unteered to participate in a tudy of nutrition as related to aging Selection from the regi trants trove to include only individuals who were phy ically and mentally capable of participating in good health not under a phy ician care within the three prior month *and not food faddi t* Selection attempted to achieve an equal ex di tribution and a range of age and eco nomic cla es Initial tudy of thi group included (a) a nutritional hi tory and a record of seven day food

intake (b) a detailed medical history and complete physical examination and (c) a series of laboratory results from blood and urine analyses and from chest x rays bone density determinations and vaginal (Papanicolaou) smears Follow up physical examinations and dietary evaluations of as many subjects as were available were made in 1952 and again in 1954 Data that have been analyzed pertain to mortality morbidity and disability (both for CVD and for total disease) in relation to the original (1948) physical findings blood analyses and diet patterns The health status of subjects still available for examination and interview is being reevaluated after a total of 11 years of observation

In 1951 a multiphasic screening examination was given to 1 000 longshoremen who volunteered to participate out of a total of 6 000 such workers in the San Francisco Bay area Tests included measurements of age height weight hearing blood pressure hemoglobin blood sugar glycosuria albuminuria a chest x ray and an ECG tracing The subsequent mortality of the 4 000 volunteers and the 2 000 nonparticipants has been followed through death certificate analyses and union health insurance records This study continues as a routine operation offering a potential for testing a series of hypotheses of causation

A health survey of a representative sample of Californians was conducted in 1954 1955 whereby information was obtained for nearly 32 000 individuals by Bureau of the Census interviewers A total of 250 individuals (150 males and 100 females) gave history of some form of CHD A substantial proportion of these individuals was matched with disease free control subjects of the same age and sex chosen from the survey population Interviews were held with diseased and control subjects to determine the relative frequencies of various characteristics that might be related to CHD (Next of kin were interviewed where subjects in the sample had died) Special attention was given to (a) smoking habits (b) presbyopia (c) physical exertion at work (d) participation in athletic events (e) occupation (f) urban versus rural residence and (g) native versus foreign birth

19 Mt Zion Hospital San Francisco Calif —The role of specific behavior patterns as they may predispose to CHD among selected population groups is under study In general these efforts measure independently (a) personality and behavioral patterns and (b) historical experiences with CHD Subjects many of whom are industrial executive were selected if they gave evidence of highly developed aggressiveness competitiveness and a tendency to accelerate all activities or if on the other hand they seemed to lack these attribute Evidence of previous experience with CHD was obtained from medical histories and ECG tracing Competitive subjects (N=83) were matched with noncompetitive subjects (N=83) by similarities in age race ethnic group diet height weight and the amount of physical activity required by their job A total of 12 unemployed blind subjects also were studied The latter resembled the noncompetitive group in personality pattern but had the complicating factor of continual anxiety At the time of observation electees first were categorized by one examiner as to whether their behavioral pattern which had been selected to represent the extreme of contrast between driving and easy going personalities were completely or incompletely developed (This was done for purpose of subclassification) A detailed medical history was taken and a physical examination performed Then a second examiner drew blood for determinations of cholesterol

and clotting time measured bleeding time and took ECG tracings. A third examiner gave detailed instructions that would permit selectees to record qualitative and quantitative information on dietary intake by daily diary technic for one week.

Short term studies on small groups of CHD patients and selected control subjects are under way to refine current technics and to develop new and better methods. Endocrine CHD hypotheses are being tested through utilization of data from urinalyses. Other studies now in progress are designed to measure personality traits by objective means. A lie detector that simultaneously records amplitude and rate of respiration, body movement and cardiac function is under study. Also a psychophysiological test is being devised in search of a predictor of the occurrence of CHD in specific groups of individuals.

20 North Dakota—In 1956-1957 a longitudinal study of CHD was started in a six county area surrounding Grand Forks, N. D., to determine the feasibility of certain investigative methods and to test specific hypotheses concerning causation of this disease. (This area was selected for study because vital records had indicated that North Dakota reported the lowest death rate from CHD in the nation.) Patients developing acute manifestations of CHD, either as new or recurrent events, were reported by practicing physicians to the study center as the primary case finding device. Also physicians provided clinical and ECG findings on their CHD patients to assist a review committee of internists in deciding whether reported cases should be considered CHD for purposes of the study and in classifying them into subgroups. Monthly visits were made by an epidemiologist to each physician in the study area and bimonthly visits were made to physicians in areas bordering the six counties to improve the degree of reporting and to collect collateral information. Hospital records and mortality statistics were reviewed periodically to check the completeness of this case finding method. A 10 per cent probability sample of dwelling units was chosen and residents therein were interviewed through Bureau of the Census enumerators for demographic and selected personal characteristics. These characteristics included data on occupation, smoking, and food habits as the principal areas of interest and were determined through personal interviews with all males aged 35 years and over who came into the probability sample. A single dietitian made detailed dietary assessments of each recognized CHD patient together with such assessments of two age matched control subjects chosen for each patient from the probability sample. Attempt was made to establish the dietary pattern of patients for the month preceding overt disease and of control subjects for the month preceding the interview. If the CHD patient had died, his wife or nearest kin was interviewed and in such instances were comparable relatives of the matched control subjects. Thereafter standardized procedures were followed in estimating qualitative and quantitative intake of specific nutrients.

21 Chicago Board of Health—An ongoing study has been conducted in a Chicago utility company in search of factors of host and environment that predispose to or precipitate cardiovascular renal morbidity and mortality, particularly ASHD and HHD. The health status, country of birth, social class, and occupational experience of 756 employees aged 50-59 years (96 per cent of the plant employees in this age class) were determined as of January 1954 from preexisting records. Using serial observation from annual physical examinations conducted through plant facilities, a series of determinative analyses is in progress. (In

intake (b) a detailed medical history and complete physical examination and (c) a series of laboratory result from blood and urine analyses and from chest x rays bone density determination and vaginal (Papanicolaou) smears Follow up physical examinations and dietary evaluations of as many subjects as were available were made in 1952 and again in 1954 Data that have been analyzed pertain to mortality morbidity and disability (both for CVD and for total disease) in relation to the original (1948) physical findings blood analyses and diet patterns The health status of subjects still available for examination and interview is being reevaluated after a total of 11 years of observation

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January 1958 the study was enlarged to include the entire labor force aged 40 59 years approximately 2 000 individuals) Specific aims include the testing of hypotheses concerning associations between CVD and the following host and environmental characteristics (a) place of birth (native or foreign born) (b) dietary habits and nutrition (c) marital status (d) physical activity (e) psychologic stress and (f) other factors

A second study concerns the comparison of Negroes and whites with respect to patterns of cholesterolemia and incidence of CHD Other correlates include age sex height weight occupation industry and duration of residence in northern states

A third study employing methods of experimental epidemiology is designed to measure the effect of a nutritional hygienic regimen on risk of developing CHD Several hundred middle aged men without evidence of CHD but presumed to be at high risk by virtue of high levels of (a) body weight (b) blood pressure and (c) serum cholesterol have been induced to follow a prescribed regimen and are being examined serially They are being contrasted for coronary disease with appropriately matched control subjects from the Chicago utility company

CO CHAIRMAN'S ADDRESS*

Herman E Hilleboe M D F A P H A

IN THE ses ions of th onference I have not heard mu h t epidemi ology or what epiden Ft eem to me we need to r the rather broad background of th are con idering I woul l t ref r to Paul Sears s commer bout a ien tist He aid Disc ry and commu nication are the two prime obli ati ns of a scienti t An o a ion such a this gives a scienti t an opportunity to ex amine some broad ues in the light of the pecial knowl dge and experi ences of tho e who are not epidemiolo gists I hope that even though our major concern is the epidemiological method applied to vari us types of heart disease we shall endeavor to think in broad terms about applying such di ci plines as mathematics physics chemis try and other sciences to the problem at hand

We hould al o bear in mind that we need to know something about biology in general and ecology in par ticular if we are to learn more about man s relation hip to his environment We have not heard much about ecolo gi ts here but I think that epidemiolo gi ts come close to being *ecologi t* in their method An ecologi t, a you know has a viewpoint ju t a little dif ferent from others in the cientific field For one thin he sees man a a social being in a cultural matrix, and powerfully affected by population dynamics

Getting down to the pecific point of epid miology I am delighted with Dr Kendall s definition of epidemiology (Report of the Subcommittee on Bio chemical Measurements) I would like to repeat it because it is tated perhaps better than many definitions made by epidemiologi ts them elves Dr Kendall aid that the purpo e of any epidemio logical tudy is to evaluate the influence of diverse genetic and environmental factors upon the occurrence and events of di ease I think this is particularly pertinent in the field of heart di ease where we have no demon trated specific etiological agents

The other remark he made that truck home had to do with differences in the mean level of particular factors that might be tati tically ignificant among di eased and control groups He pointed out that values for the two groups are scattered over the same range and have little diagnostic or prognostic ignificance for any given individual I would like to reempha ize that, tr ctly peaking urveys of characteri t cs are not epidemiological studies they do not relate the di ea e to specif environ mental or genetic factors which charac terize the populations under investi a tion He pointed out that in many tudies biochemical determinations have been ub tituted either for an adequate tudy of the factors or for an *ultimate* apprai al of the clinical manifestations of the disease

In the area of epidemiology and par ticularly in heart disease *there* are several things that need to be said *about* the viewpoint of those who *work in* epidemiology and who have epidemio logical tudies going on in are

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On the third day of the Conf r nce

such as heart disease, cancer, automobile accidents, cerebral palsy, and birth defects. All these studies have a common denominator. I think it is particularly important that we talk about the methods of epidemiology because intrinsic in these studies is the use of statistical method.

Unfortunately, certain groups in our country feel strongly that statistical studies on man are of relatively little value and inconclusive. These groups believe that the true facts can be ascertained only by animal experimentation and clinical observation. This is not said in criticism—this is merely an observation. We are often urged to take no public health action until laboratory and clinical studies have given ultimate answers about the nature of such disease as cancer. This attack on the public health approach expresses a belief that is widely held. I think perhaps for that reason it is important to point out that epidemiological studies on man have been highly productive of scientific knowledge and of practical application in the advance of medical science. This does not in any way deprecate the value of animal experimentation in the laboratory or clinical investigation in the ward. I think these things are indispensable and certainly necessary for medical progress. But we must emphasize the true value of the epidemiological approach with its heavy reliance on statistical compilation in the analysis of events that occur in human population.

I would like to make another point here that has not been mentioned in the last two days of discussion, and that is the interchangeability of medical statisticians and epidemiologists. The medical statistician is usually called a biostatistician and is first of all a mathematician who adapts his knowledge to the study of disease. The epidemiologist, on the other hand, is skilled in medicine but has learned to adopt a mathematical approach in the study of disease among groups of people. Certainly, whenever possible, the two work together; in the process the statistician becomes a better epidemiologist and the epidemiologist a better statistician, so that the two ultimately approach one another closely in their skills. Since the distinguishing feature of an epidemiological study is its use of numbers and their analysis by statistical method and logic, it seems permissible in the present discussion and in our future discussions in this area to use the words biostatistics and epidemiology almost interchangeably.

Without going into great detail, I think it would be wise for all of us interested in epidemiology to go back to the era preceding knowledge of the bacterial and viral causes of disease to see the way in which some of the early workers used epidemiological methods. When Jenner did his work on smallpox 161 years ago he handled his accounts and compiled his cases in such a way that he really carried out a neat epidemiological study. He knew nothing about the cause of the disease and yet he found out how to prevent the disease. John Snow's classic studies on cholera in 1854 are a parallel with what we are facing today in heart disease. Many of the same puzzles were faced by John Snow in his attempt to work out the relationships between cholera and the way in which the disease was transmitted. Michael Taylor in England studied epidemics of typhoid fever in 1857 and traced its transmission through milk. Again he knew little about the cause, but he knew how to develop meaningful associations. So as we trace epidemics back through the last century we find many individual investigators confronted with precisely the same types of problems that we are facing at the present time in heart disease.

To bring this viewpoint up to date, I should like to point out that our

knowledge of carcinogenic agents and the means of preventing certain types of *neoplastic disease to the extent that* we can is largely the product of epidemiological studies. Certainly the early studies on scrotal cancer in chimney sweeps, on cancer from contact with spindle oil, on cancer of the bladder of aniline workers and on skin cancer from arsenic are all examples of the epidemiological approach. Many of you are familiar with some of the recent reports on the development of leukemia among those treated with x-rays for spondylitis, the effects on children of irradiation of the thymus, and the increase of congenital deformities among babies whose mothers had pelvic x-ray examination during pregnancy. Again these are examples of the method we are talking about.

I would like to read a short quotation from Dr. Frost, one of our foremost epidemiologists, who was my professor of epidemiology at the Johns Hopkins School of Hygiene and Public Health. He said: "The opinion is more or less *prevalent that inference based upon epi*demiological argument cannot be truly conclusive because the evidence is purely circumstantial. Such opinion has frequently failed to take account of the whole mass of evidence and to follow the argument which is necessarily built up step by step in its somewhat complex and perhaps tedious way. Given sufficient scope and accuracy of observation, a conclusion as to the nature and spread of disease may often be established quite firmly by circumstantial evidence well in advance of experimental confirmation. Moreover many problems of disease transmission which are highly important from the standpoint of prevention are of a type that can be solved only by investigation of this kind. The weakness in conclusions drawn from circumstantial studies is usually chargeable not to basic defect in the method of investigation but more often to paucity or inaccuracy of data or to false logic in their inter*pretation*."

Finally, I would like to say that in talking about epidemiology we must be cautious about the use of the word. We hear about shoeleather epidemiologists who go out into the field and learn things by doing their own work. We hear about armchair epidemiologists who have others gather their data. Now we have heard recently about clinical epidemiology. Dr. John Paul of Yale has just published a book* with that title. We hear also of experimental epidemiology. The point I wish to make here is that we need to consider epidemiology in its total context.

We also need to realize that many heart disease studies labeled epidemiological do not actually follow epidemiological methods in their design or execution. There is no reason why every study which sets out to describe characteristics of persons with heart disease should be called an epidemiological study. It is my hope that when *clinical and laboratory* researchers design and carry out epidemiological studies they take care to study carefully and follow epidemiological method. Only when a study employs epidemiological method should it be labeled epidemiological.

Good epidemiological studies are very difficult in coronary heart disease because the preclinical stages of atherosclerosis—the precursor of coronary heart disease—appear to be occurring almost universally among our adult population in the United States. When a disease is almost universal the comparison of cases and noncases become almost impossible except in post mortem studies. Yet the comparison of cases with noncases comprises the basic method of epidemiology.

Difficulties notwithstanding, there re

*Paul, John R.: Clinical Epidemiology. University of Chicago Press, 1958.